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Total synthesis and cytotoxic activity of 5′-hydroxyzearalenone and 5′β-hydroxyzearalenone

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ABSTRACT

An efficient and convergent synthesis of 5′-hydroxyzearalenone and 5′β-hydroxyzearalenone, 14-membered β-resorcylic acid lactone (RAL) natural products, has been achieved in 19 longest linear and 29 total steps starting from commercially available 5-hexen-1-ol and methyl 2-(3,5-dimethoxyphenyl)acetate. The key features of our synthesis include the Jacobsen hydrolytic kinetic resolution, Mitsunobu esterification and *E*-selective ring-closing metathesis (RCM). Our synthesis also highlights the utility of the acetal protecting group of the resorcylate moiety and its compatibility in RCM for synthesis of 14-membered RALs. Cytotoxic activity of both synthetic compounds against seven human cancer cell lines was evaluated. 5′-Hydroxyzearalenone exhibits more potent cytotoxic activity against most of cancer cell lines tested than its epimer, 5′β-hydroxyzearalenone. Both compounds display significant cytotoxic activity against the C33A cervical cancer cell line with IC_{50} values of 21.33 ± 6.43 μM and 16.00 ± 12.17 μM, respectively.

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Introduction

Resorcylic macrolides are a group of fungal polyketide metabolites consisting of 14-membered resorcylic acid lactone (RAL) derivatives that possess diverse pharmacological profiles.[1] Selected examples of these macrolides are zearalenone (**1**),[2] radicicol (**2**),[3] hypothemycin (**3**),[4] and aigialomycin D (**4**)[5] (Figure 1). These RALs have been shown to exhibit cytotoxic,[6] antifungal,[7] antiplasmodial,[8] antifouling[9] and antiviral against Herpes Simplex Virus 1 (HSV1)[10] activities as well as estrogen antagonism[11] and inhibitory effects against ATPases and kinases.[12] Owing to their impressive profiles of biological activity, this class of macrolides has attracted considerable interest as a target for total chemical synthesis from many synthetic groups worldwide.[1]

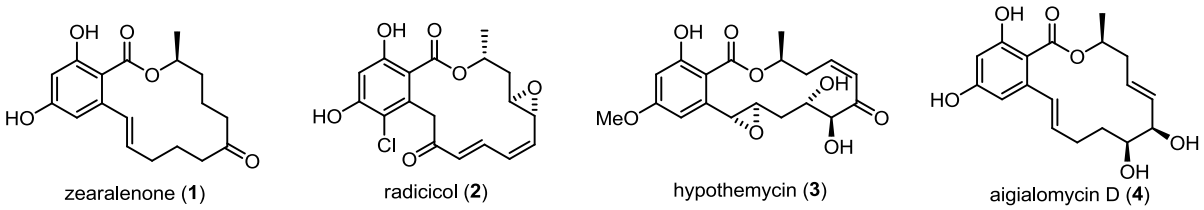


Figure 1. Examples of resorcylic acid lactone natural products.

5′-Hydroxyzearalenone (**5**) and 5′β-hydroxyzearalenone (**6**) are new 14-membered β-resorcylic macrolides isolated from the seagrass-derived fungi *Fusarium* sp. PSU-ES73 by Arunpanichlert et al. in 2011 and *Fusarium* sp. PSU-ES123 by Saetang et al. in 2016, respectively (Figure 2).[13,14] Structurally, compounds **5** and **6** are 5′-hydroxy analogues of zearalenone and consist of two stereogenic centers at the 5′ and 10′-positions. The absolute configuration of C10′ of **5** and **6** was proposed to be *S* based on the well-established absolute configuration at this chiral center of zearalenone natural product analogues and comparison of the negative Cotton effect at 266 nm with that of 3*R*,5*S*-sonnerlactone.[15] The absolute configuration of the alcohol stereogenic center at the 5′-position of **5** and **6** was assigned based on the Mosher ester analysis. Due to paucity of materials and promising biological activities of this class of natural products, we became interested in synthesizing 5′-hydroxy- (**5**) and 5′β-hydroxyzearalenones (**6**) in order to confirm the absolute stereochemistry of the natural products and to provide materials for further biological activity evaluation. Herein, we describe efficient and convergent syntheses of both natural products and evaluation of their cytotoxic activity against seven human cancer cell lines.

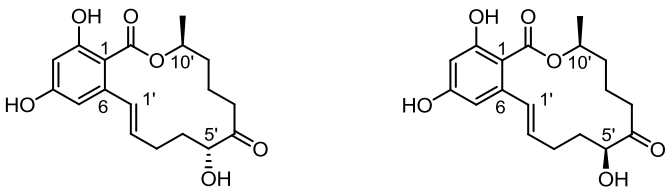
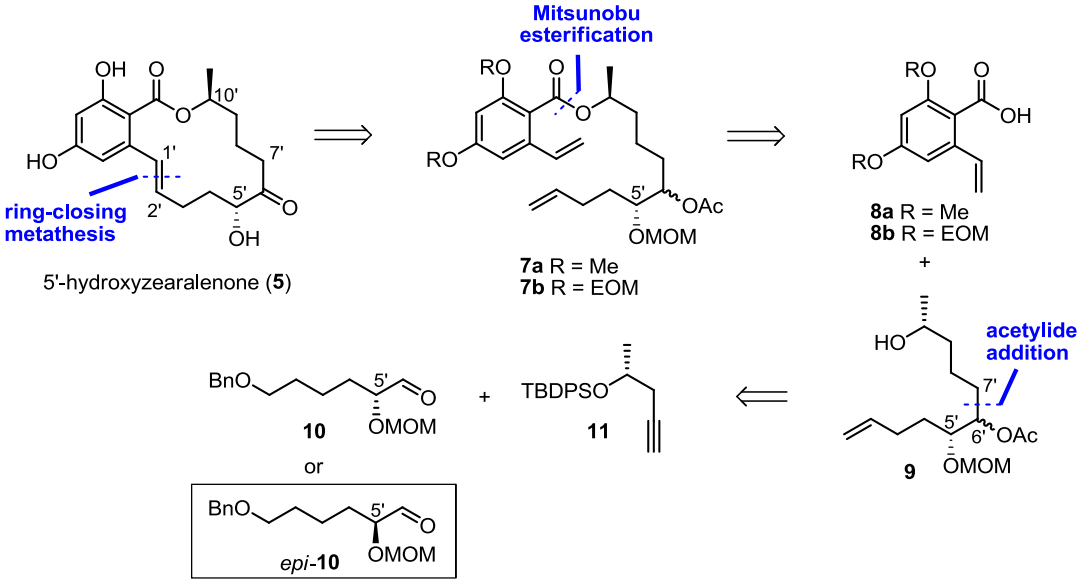


Figure 2. Structures of 5′-hydroxy- (**5**) and 5′β-hydroxyzearalenones (**6**).

Results and discussion

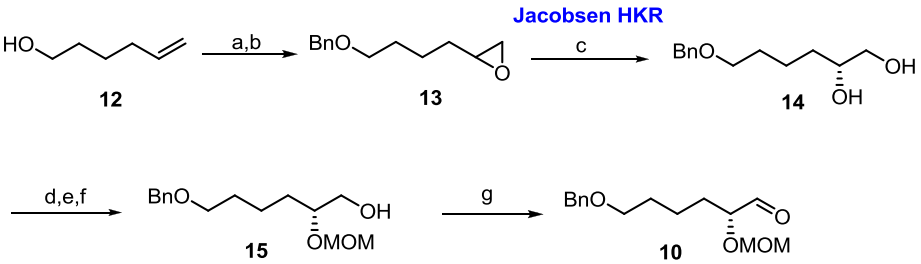
A retrosynthetic analysis of **5** and **6** is outlined in Scheme 1. We relied on the well-precedented ring-closing metathesis (RCM)[16,17] as a key macrocyclization and to establish the (*E*)-geometry of C1′–C2′ olefin. The RCM diene precursor **7a** or **7b** would be assembled by Mitsunobu esterification[16a-e] between benzoic acid derivative **8a** or **8b** and advanced alcohol intermediate **9**. Alcohol **9** would be constructed by addition of the corresponding acetylide of known alkyne **11**[18] to chiral aldehyde **10**. We envisioned that synthesis of the 5′β-hydroxyzearalenone (**6**) would be viable via the same strategy starting from the enantiomer of **10** (*epi*-**10**).



Scheme 1. Retrosynthetic analysis of 5′-hydroxy- (**5**) and 5′β-hydroxyzearalenones (**6**).

The synthesis of chiral aldehyde **10** is illustrated in Scheme 2. We utilized the Jacobsen hydrolytic kinetic resolution (HKR) to install the stereogenic center in **10**.[19] The synthesis of **10** commenced with protection of commercially available 5-hexen-1-ol (**12**) with a benzyl (Bn) group, followed by epoxidation of the corresponding alkene with *m*-CPBA to

yield racemic epoxide **13**.[20] Hydrolytic kinetic resolution of **13** using (*S*,*S*)-Co(III)(salen)(OAc) catalyst resulted in the formation of (*R*)-diol **14** in 45% yield (88% ee). Selective protection of the secondary alcohol moiety of diol **14** was achieved in 3 steps: benzoylation of the primary alcohol, protection of the secondary alcohol with methoxymethyl (MOM) group and removal of the benzoate group using K_2CO_3 in MeOH to give alcohol **15** in 73% over three steps. The absolute configuration of the alcohol chiral center was confirmed by the Mosher ester analysis of the corresponding benzoate (see Supporting Information). Subsequent oxidation of **15** with $PhI(OAc)_2$ in the presence of catalytic TEMPO smoothly gave the desired chiral aldehyde **10** in 87% yield.



Scheme 2. Synthesis of chiral aldehyde **10**. Reagents and conditions: (a) NaH, BnBr, THF, 0 °C to rt, 78%; (b) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 93%; (c) (*S*,*S*)-Co(III)(salen)(OAc), H_2O, 0 °C to rt, 45% (88% ee); (d) BzCl, Et_3N, CH_2Cl_2, 0 °C to rt; (e) MOMCl, EtN(*i*-Pr)$_2$, toluene/CH_2Cl_2, 0 °C to rt; (f) K_2CO_3, MeOH, 73% over 3 steps; (g) $PhI(OAc)_2$, cat TEMPO, CH_2Cl_2, rt, 87%.

We next focused on the key acetylide addition to construct the C6′–C7′ bond of alcohol intermediate **9** (Scheme 3). Addition of the acetylide generated *in situ* by deprotonation of alkyne **11** with *n*-BuLi to aldehyde **10** afforded propargylic alcohol **16** as a mixture of diastereomers in 81% yield based on recovered starting aldehyde.[18] The diastereoselectivity of this addition was inconsequential as the C6′ stereogenic center would eventually be oxidized to the corresponding ketone. The newly generated alcohol **16** was then protected with Ac_2O to give the corresponding acetate ester **17**. Reduction of alkyne and concomitant removal of the benzyl protection group under catalytic hydrogenation in ethanol provided alcohol **18** in 75% yield. Conversion of the resultant alcohol **18** to the corresponding alkene was accomplished in 2 steps via iodination using I_2, PPh_3 and imidazole and subsequent elimination with KO*t*-Bu in THF at 0 °C. It should be noted that excess (3.5 equivalents) KO*t*-Bu was required to ensure complete consumption of the starting iodide,

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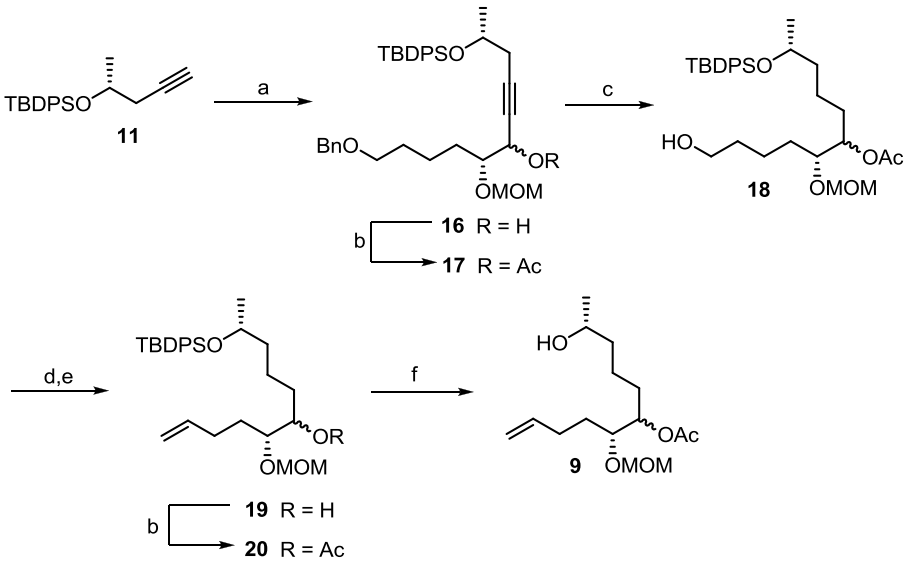
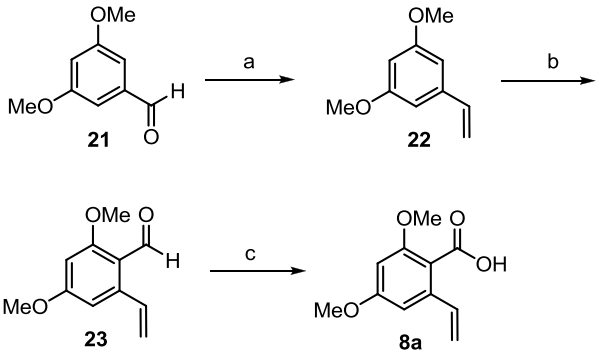
nevertheless, the acetyl protecting group was simultaneously removed in this step. Thus, alcohol **19** was reprotected with the Ac group under previously described conditions to give ester **20** in 98%. Finally, deprotection of the TBDPS group with TBAF in THF smoothly gave the requisite alcohol intermediate **9** in 83% yield.



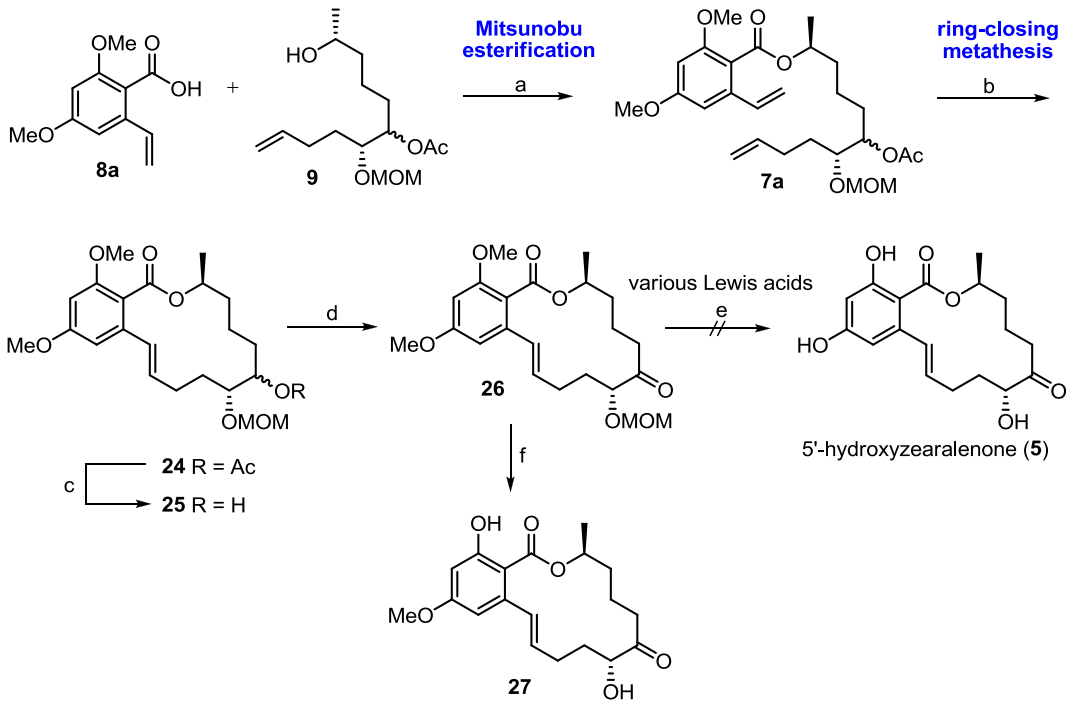
Scheme 3. Synthesis of advanced alcohol intermediate **9**. Reagents and conditions: (a) *n*-BuLi, THF, –78 °C to –30 °C then **10**, –78 °C to 0 °C, 81% based on recovered aldehyde (21%); (b) Ac_2O, Et_3N, cat DMAP, CH_2Cl_2, rt, 97% for **17**, 98% for **20**; (c) H_2, Pd/C, EtOH, rt, 75%; (d) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 93%; (e) KO*t*-Bu, THF, 0 °C to rt, 89%; (f) TBAF, THF, 0 °C to rt, 83%.

For the synthesis of benzoic acid derivative as a Mitsunobu coupling partner, we initially chose the methyl protecting groups for the phenol moieties. The known benzoic acid derivative **8a** was prepared according to the procedure reported by Nanda and Jana[16c] under slightly modified conditions as illustrated in Scheme 4. Wittig olefination of 3,5-dimethoxybenzaldehyde (**21**) using methyltriphenylphosphonium bromide and *n*-BuLi provided styrene **22** in 96% yield. Vilsmeier-Haack reaction of **22** using oxalyl chloride as an activating agent instead of $POCl_3$ introduced the formyl group in the position *ortho* to the vinyl substituent to give unstable benzaldehyde **23** in 94% yield. Lastly, Pinnick oxidation of **23** furnished the desired benzoic acid **8a** in 76% yield.[17c,21]



Scheme 4. Preparation of benzoic acid derivative **8a**. Reagents and conditions: (a) Ph_3PCH_3Br, *n*-BuLi, THF, 0 °C, 96%; (b) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 94%; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 76%.

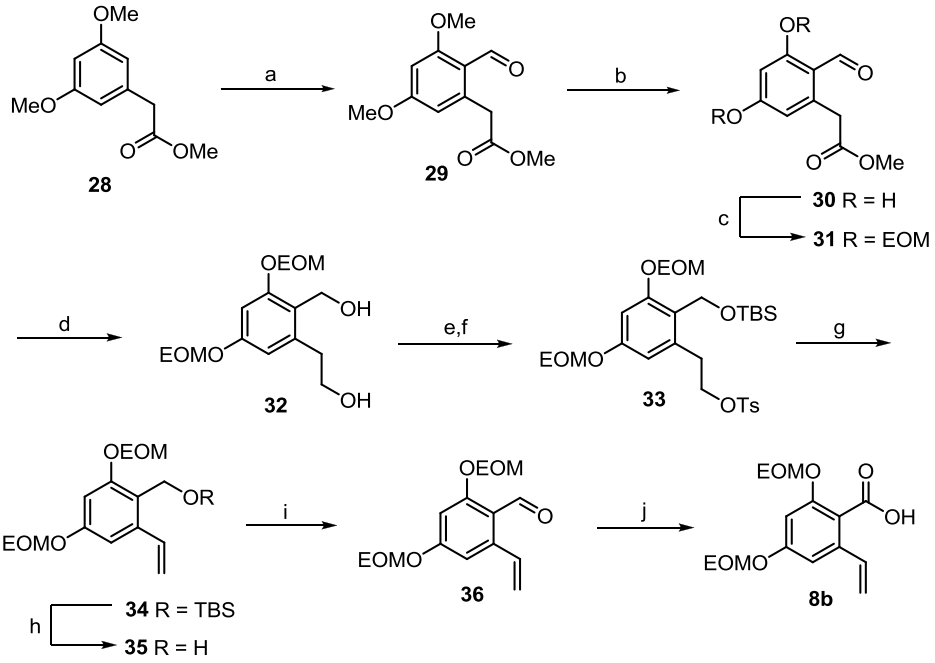
With both benzoic acid derivative **8a** and alcohol **9** in hand, the stage was then set for union of the two fragments under Mitsunobu esterification conditions (DIAD, PPh_3)[17c], which afforded ester diene **7a** in good yield (Scheme 5). This Mitsunobu esterification step should also provide the correct stereochemistry of the C2′ stereogenic center of the natural product. Gratifyingly, ring-closing metathesis of **7a** in the presence of second-generation Grubbs catalyst (5 mol %) in toluene (3.5 mM) at 80 °C provided the desired macrocycle **24** in 74% yield as a separable 1.5:1 mixture of diastereomers.[16b,17c] The *E*-geometry of the newly generated C1′–C2′ olefin was confirmed based on the coupling constant of 15.7 Hz between H1′ and H2′ of the minor diastereomer. Removal of the acetate protecting group of each diastereomer with K_2CO_3 in methanol smoothly produced alcohol **25** in good yield. Subjection of each diastereomer of **25** to Dess-Martin periodinane (DMP) oxidation in CH_2Cl_2 resulted in the formation of the identical ketone **26** in excellent yields (88% for the major diastereomer and 85% for the minor diastereomer). Unfortunately, attempts to globally remove both methyl protecting groups on the aromatic ring and the MOM group using various Lewis acids e.g. BCl_3,[22] BBr_3[23] and $AlCl_3$ were unsuccessful and led to unidentified complex mixture or decomposition. Previous reports by Maier[17a, b], Yadav[17c] and Minnaard[17d] have demonstrated the successful deprotection of both methyl groups on the resorcylate moieties in the synthesis of some 14-membered RALs. However, in our case when treating macrocycle **26** with AlI_3 in benzene at 0 °C, 4-O-methyl 5′-hydroxyzearalenone (**27**) was obtained as a major isolated product in 25% yield.[17] Attempt to remove the remaining Me group on the aromatic ring of **27** by further treatment with AlI_3 led to decomposition.



Scheme 5. Attempted synthesis of 5′-hydroxyzearalenone (**5**). Reagents and conditions: (a) DIAD, PPh_3, toluene, rt, 71%; (b) Grubbs II (5 mol %), toluene, 80 °C, 74% (major:minor = 1.5:1); (c) K_2CO_3, MeOH, rt, 81% for major isomer, 82% for minor isomer; (d) DMP, CH_2Cl_2, rt, 88% for major isomer, 85% for minor isomer; (e) i. BCl_3, CH_2Cl_2, 0 °C; ii. BCl_3, CH_2Cl_2, –78 °C; iii. BBr_3, CH_2Cl_2, 0 °C; iv. BBr_3, CH_2Cl_2, –78 °C; v. $AlCl_3$, CH_2Cl_2, 0 °C; (f) AlI_3, benzene, 0 °C, 25%.

To circumvent the methyl deprotection problems, we decided to switch the phenol protecting groups from methyl to ethoxymethyl (EOM) groups for the purpose of final global deprotection by simply treating with HCl. The synthesis of benzoic acid derivative **8b** was achieved in 10 steps from commercially available methyl 2-(3,5-dimethoxyphenyl)acetate (**28**) (Scheme 6). Phenol **30** was prepared in 2 steps from **28** according to a procedure reported by Dong et al. under slightly modified conditions.[24] EOM ether **31** was achieved by reprotection of the free phenol moieties of **30** with EOMCl. To convert ester **31** to the desired styrene derivative, we proceeded with reduction of both carbonyl groups of **31** using excess $NaBH_4$ in a mixture of MeOH and THF to afford diol **32** in quantitative yield and no chromatographic purification. Selective tosylation of the presumably less sterically hindered hydroxyl group of **32** with 1 equivalent of tosyl chloride resulted in the formation of the desired monotosylate albeit in 37% yield. Due to poor stability of the resulting tosylate, it was immediately used in the next step to protect the remaining hydroxyl group with *t*-butyldimethylsilyl chloride

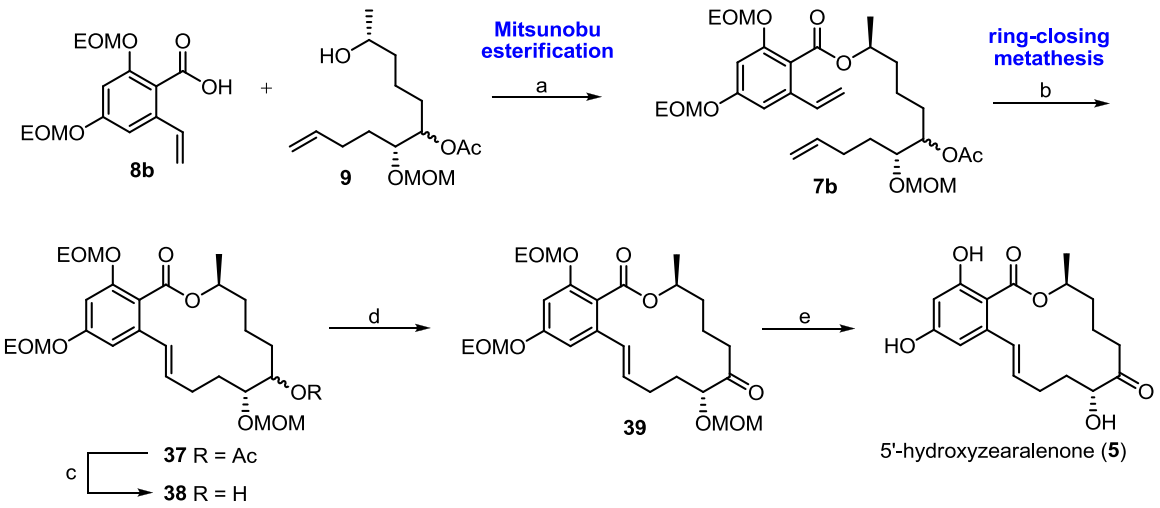
(TBSCl), which delivered silyl ether **33** in 71% yield. Subsequent elimination of tosylate **33** with KO*t*-Bu in THF at 0 °C furnished styrene **34** in 85% yield. Removal of the TBS group was accomplished by treating **34** with TBAF to give alcohol **35** in 93% yield. The hydroxyl group of **35** was then converted to carboxylic acid via benzaldehyde **36** by IBX oxidation, followed by Pinnick oxidation to afford the desired benzoic acid **8b** in 81% yield.[17c,21]



Scheme 6. Preparation of benzoic acid derivative **8b**. Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 70% (and 12% of isomeric formylated product); (b) $AlCl_3$ CH_2Cl_2, reflux, 98%; (c) EOMCl, EtN(*i*-Pr)$_2$, cat DMAP, CH_2Cl_2, 0 °C to rt, 84%; (d) $NaBH_4$, MeOH/THF, 0 °C to rt, quant.; (e) TsCl, Et_3N, cat DMAP, CH_2Cl_2, 0 °C to rt, 37%; (f) TBSCl, imidazole, cat DMAP, CH_2Cl_2, 0 °C, 71%; (g) KO*t*-Bu, THF, 0 °C to rt, 85%; (h) TBAF, THF, 0 °C to rt, 93%; (i) IBX, toluene/DMSO, 96%; (j) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 0 °C to rt, 81%.

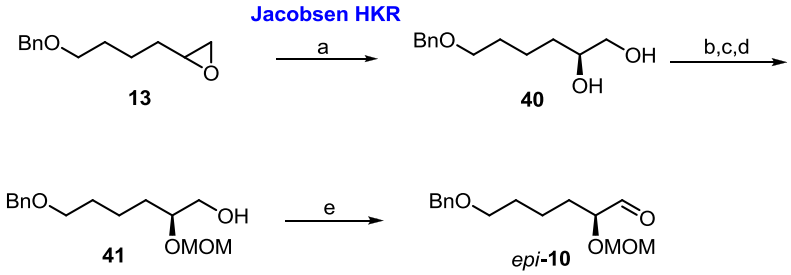
The benzoic acid derivative **8b** and alcohol intermediate **9** were subjected to the Mitsunobu esterification conditions[16c],which afforded ester diene **7b** in 70% yield (Scheme 7). To our delight, ring-closing metathesis of **7b** in the presence of second-generation Grubbs catalyst (10 mol %) in refluxing CH_2Cl_2 at high dilution (2 mM) provided the desired macrocycle **37** in a remarkable 87% yield as separable diastereomers (major:minor = 1.7:1).[16c] The geometry of the resulting C1′–C2′ olefin of the macrocylic product was confirmed by the coupling constant of 15.9 Hz between H1′ and H2′ of the minor

diastereomer of **37**. However, no attempts were made to assign the absolute configuration of the C6′ stereogenic center since it would be oxidized to ketone in the penultimate step of the synthetic sequence. We then proceeded with removal of the acetate protecting group of each diastereomer with K_2CO_3 in methanol, which smoothly produced alcohol **38** in good yield. As anticipated, subjection of each diastereomer of **38** to DMP oxidation in CH_2Cl_2 at room temperature led to the identical ketone **39**. This step also confirmed that our RCM conditions gave (*E*)-olefin exclusively. Finally, global deprotection of both EOM groups on the aromatic ring and the MOM group using concentrated HCl in MeOH at 0 °C produced 5′-hydroxyzearalenone in 62% yield. The ^1H and ^{13}C NMR spectroscopic data as well as HRMS data of synthetic 5′-hydroxyzearalenone (**5**) were in good agreement with those reported for natural **5** (see Supporting Information). The specific rotation of synthetic **5** was observed as $[\alpha]_D^{28}$ –25.9 (*c* 0.10, acetone), which was nearly identical to that of the natural product **5** ($[\alpha]_D^{25}$ –29.5, *c* 1.00, acetone).[13] The circular dichroism (CD) spectrum of synthetic **5** showed a negative Cotton effect at 266 nm, confirming the *S* configuration of the C10′ stereogenic center analogous to that reported by Lin and co-workers.[15] Our synthesis thus verified the absolute configuration of the natural product.

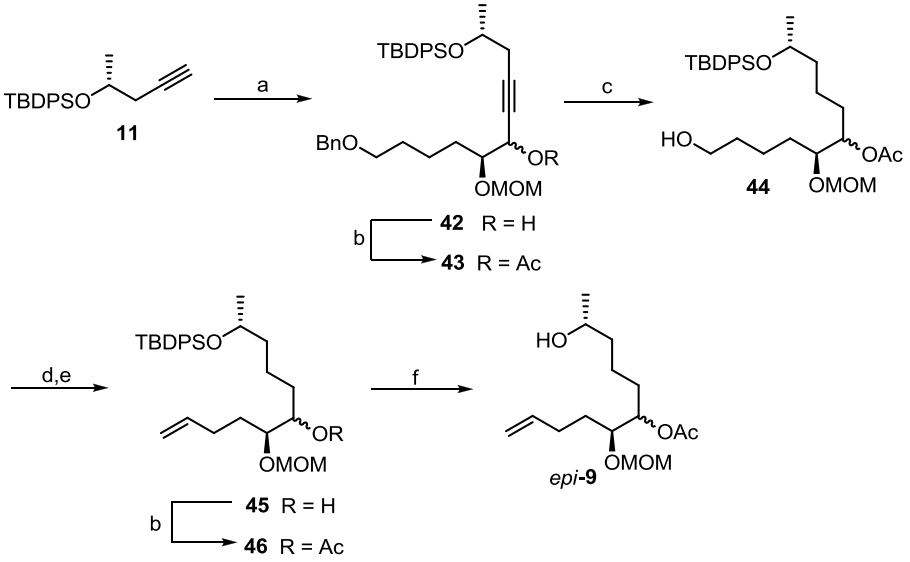


Scheme 7. Completion of the synthesis of 5′-hydroxyzearalenone (**5**). Reagents and conditions: (a) DIAD, PPh_3, toluene, rt, 70%; (b) Grubbs II (10 mol %), CH_2Cl_2, 45 °C, 87% (major:minor = 1.7:1); (c) K_2CO_3, MeOH, rt, 76% for major isomer, 70% for minor isomer; (d) DMP, CH_2Cl_2, rt, 83% for major isomer, 81% for minor isomer; (e) conc HCl, MeOH, 0 °C to rt, 62%.

The natural product 5′β-hydroxyzearalenone (**6**) was synthesized via the same strategy starting from chiral aldehyde *epi*-**10**. Hydrolytic kinetic resolution of epoxide **13** in the presence of (*R*,*R*)-Co(III)(salen)(OAc) catalyst afforded (*S*)-diol **40** in 45% yield (94% ee) (Scheme 8). Chiral aldehyde *epi*-**10** was thus prepared in 4 steps from (*S*)-diol **40** using the previously described protocol. Aldehyde *epi*-**10** was further elaborated to the desired alcohol *epi*-**9** in 7 steps utilizing the same synthetic sequence outlined in Scheme 9.



Scheme 8. Synthesis of chiral aldehyde *epi*-**10**. Reagents and conditions: (a) (*R*,*R*)-Co(III)(salen)(OAc), H_2O, 0 °C to rt, 45% (94% ee); (b) BzCl, Et_3N, CH_2Cl_2, 0 °C to rt; (c) MOMCl, EtN(*i*-Pr)$_2$, toluene/CH_2Cl_2, 0 °C to rt; (d) K_2CO_3, MeOH, 72% over 3 steps; (e) PhI(OAc)$_2$, cat TEMPO, CH_2Cl_2, rt, 93%.



Scheme 9. Synthesis of alcohol *epi*-**9**. Reagents and conditions: (a) *n*-BuLi, THF, –78 °C to –30 °C then *epi*-**10**, –78 °C to 0 °C, 83% based on recovered aldehyde (22%); (b) Ac_2O, Et_3N, cat DMAP, CH_2Cl_2, rt, 97% for **43** and **46**; (c) H_2, Pd/C, EtOH, rt, 66%; (d) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 94%; (e) KO*t*-Bu, THF, 0 °C to rt, 96%; (f) TBAF, THF, 0 °C to rt, 76%.

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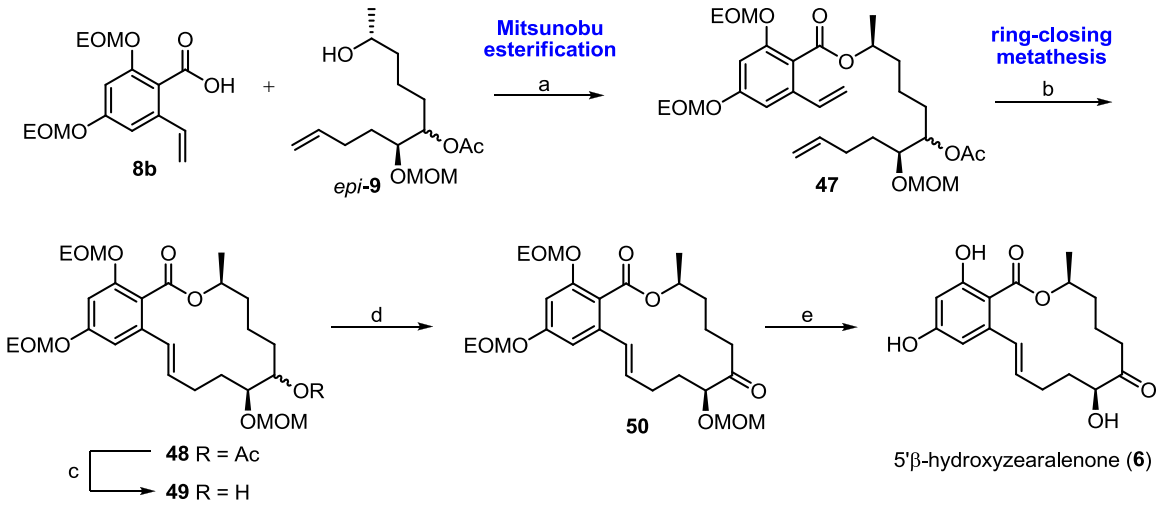
Completion of the synthesis of 5′β-hydroxyzearalenone (**6**) was achieved via the same synthetic sequence as that of **5** (Scheme 10). Mitsunobu esterification reaction between benzoic acid **8b** and alcohol *epi*-**9** furnished the desired ester **47** in 70% yield. The ring-closing metathesis of diene **47** using second-generation Grubbs catalyst (10 mol %) in refluxing CH_2Cl_2 (2 mM) produced the macrocyclic product **48** in 65% yield as an inseparable mixture of diastereomers. It should be noted that the geometry of the resulting C1′–C2′ olefin could not be determined at this point. We then carried these diastereomeric mixtures to the next step, which was acetyl group deprotection by treatment with K_2CO_3 in MeOH. Gratifyingly, these alcohol products **49** could be separated by silica gel column chromatography to result in a 1.3:1 ratio of diastereomers and 77% combined yield. We also confirmed the geometry of C1′–C2′ olefin to be *E* from the coupling constant (16.2 Hz) between H1′ and H2′ of each diastereomer. Each diastereomer of **49** was subsequently oxidized with DMP in CH_2Cl_2 to furnish the identical ketone **50** (88% for the major diastereomer and 79% for the minor diastereomer). Similarly, global deprotection of both EOM and the MOM groups of **50** under the same conditions to those of **39** delivered 5′β-hydroxyzearalenone (**6**) in 75% yield. The ^{1}H and ^{13}C NMR spectroscopic and HRMS data of synthetic **6** were in good agreement with those reported for natural product **6** (see Supporting Information). The specific rotation of synthetic **6** ($[\alpha]_D^{28}$ –97.4, *c* 0.10, acetone) was in accordance with the reported value for the natural product **6** ($[\alpha]_D^{25}$ –65.0, *c* 1.00, acetone).[14] Similarly, the CD spectrum of synthetic **6** displayed a negative Cotton effect at 266 nm, which confirmed the absolute configuration of the natural product.



Scheme 10. Completion of the synthesis of 5′β-hydroxyzearalenone (**6**). Reagents and conditions: (a) DIAD, PPh_3, toluene, rt, 70%; (b) Grubbs II (10 mol %), CH_2Cl_2, 45 °C, 65%; (c) K_2CO_3, MeOH, rt, 77% (major:minor = 1.3:1); (d) DMP, CH_2Cl_2, rt, 88% for major isomer, 79% for minor isomer; (e) conc HCl, MeOH, 0 °C to rt, 75%.

Synthetic compounds **5** and **6** were subjected to cytotoxic activity evaluation against seven human cancer cell lines including two breast adenocarcinoma (MDA-MB-231 and MCF-7), three cervical carcinoma (C33A, HeLa and SiHa), one hepatoma (HepG2) and one colorectal carcinoma (HCT116) cells by MTT assay (Table 1 and Figure 3). It was observed that both compounds could inhibit the proliferation of all cancer cell lines with the IC_{50} ranges of 21.33–53.00 μM for compound **5** and 16.00–179.33 μM for compound **6**, albeit in lower extent compared to standard drugs cisplatin and doxorubicin (Table 1). It should be noted that 5′-hydroxyzearalenone (**5**) showed more potent cytotoxic activity against most of cancer cell lines than its epimer, 5′β-hydroxyzearalenone (**6**). Among the seven cancer cell lines tested, the C33A was the most sensitive cell to both compounds **5** and **6** with IC_{50} values of 21.33 ± 6.43 μM and 16.00 ± 12.17 μM, respectively. Interestingly, although compounds **5** and **6** are concomitantly toxic to noncancerous Vero cells even at a lower concentration (50 μM), these two compounds at 200 μM preferentially reduced the viability of C33A (9.46% and 10.71%, respectively) and HepG2 (12.38% and 9.28%, respectively) cells more than 2-fold compared to Vero cells (25.05% and 29.23%, respectively) (Figure 3).

Table 1. Cytotoxic activity of 5′-hydroxy- (**5**) and 5′β-hydroxyzearalenones (**6**) against seven human cancer cell lines.

cell lines	**Cytotoxicity, IC_{50} (μM)**			
	5	**6**	**cisplatin**	**doxorubicin**
MDA-MB-231	53.00 ± 4.36	119.33 ± 18.04	41.00 ± 1.73	0.045 ± 0.001
MCF-7	44.00 ± 5.29	110.00 ± 2.00	>50	0.048 ± 0.000
HCT116	41.33 ± 5.77	60.00 ± 3.46	45.67 ± 1.15	0.048 ±0.000
HepG2	42.67 ± 2.31	112.67 ± 10.26	19.00 ± 1.73	0.0046 ± 0.000
C33A	21.33 ± 6.43	16.00 ± 12.17	7.00 ± 1.00	0.038 ± 0.000

HeLa	50.00 ± 4.00	128.00 ± 7.21	16.67 ± 2.31	0.042 ± 0.001
SiHa	48.00 ± 7.21	179.33 ± 9.02	15.33 ± 2.52	0.046 ± 0.001
Vero	41.33 ± 2.31	43.33 ± 3.06	8.00 ± 0.00	0.058 ± 0.001

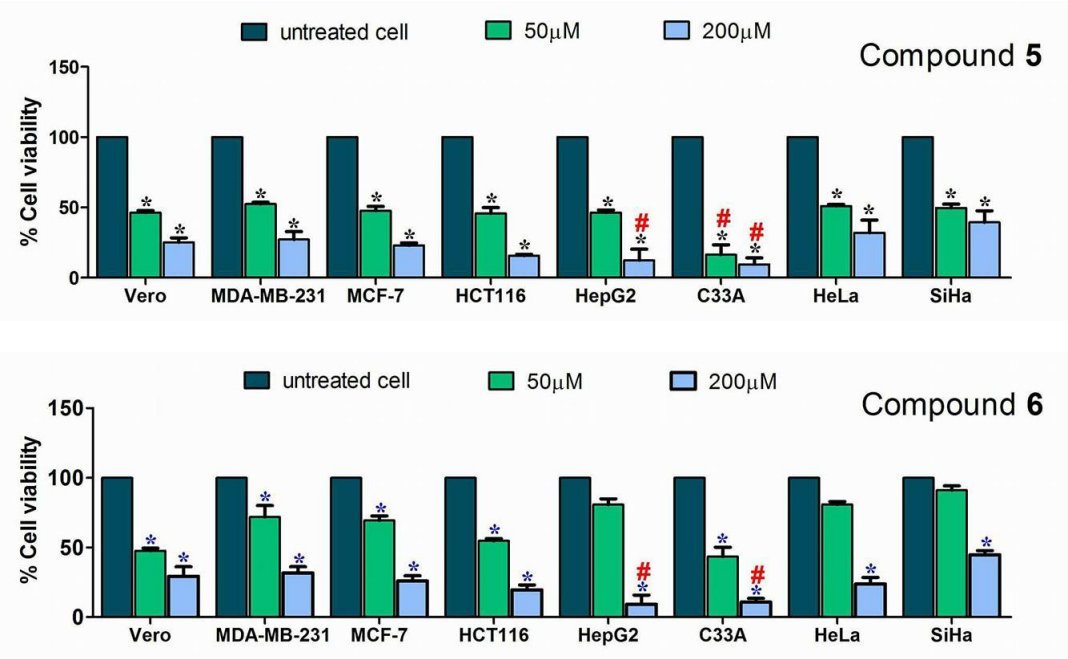


Figure 3. Viability of cells treated with compounds **5** and **6** at 50 and 200 μM for 72 h as determined by MTT assay. Results are shown as percentages of cell viability relative to untreated cell (0.2% (v/v) DMSO). Data are expressed as means ± SD. Statistical significance was accepted at $p<0.05$ when (*) was compared between treated and untreated cells, and (#) between cancer and Vero cells under the same treatment.

Conclusions

In summary, we have developed an efficient and convergent synthesis of 5′-hydroxyzearalenone (**5**) and 5′β-hydroxyzearalenone (**6**) starting from commercially available 5-hexen-1-ol and methyl 2-(3,5-dimethoxyphenyl)acetate. The synthesis was achieved in 19 longest linear and 29 total steps and 2.0% and 1.8% overall yields for **5** and **6**, respectively. The key features of our synthesis include the Jacobsen hydrolytic kinetic resolution to install the C5′ stereogenic center, Mitsunobu esterification to couple the key fragments and ring-closing metathesis to construct the macrocycle and establish the (*E*)-geometry of the C1′–C2′ olefin. Our synthesis also highlights the utility of acetal protecting group of the resorcylate moiety and its compatibility in the ring-closing metathesis reaction

for synthesis of 14-membered RALs, which allows for mild deprotection that is not detrimental to sensitive functional groups. Synthetic compounds **5** and **6** were evaluated for cytotoxic activity against seven human cancer cell lines. It was observed that the α-epimer **5** showed more potent cytotoxic activity against most of cancer cell lines tested than the β-epimer **6**. Both compounds **5** and **6** showed significant cytotoxic activity against the C33A cervical cancer cell lines with IC_{50} values of 21.33 ± 6.43 μM and 16.00 ± 12.17 μM, respectively.

Experimental Section

General information: Unless otherwise stated, all reactions were conducted under a nitrogen or argon atmosphere in oven- or flamed-dried glassware. Solvents were used as received from suppliers or distilled prior to use using standard procedures. All other reagents were obtained from commercial sources and used without further purification. Column chromatography was performed on SiliaFlash® G60 Silica (60-200 μm, Silicycle) or Silica gel 60 (0.063-0.200 mm, Merck). Thin-layer chromatography (TLC) was performed on SiliaPlate™ R10011B-323 (Silicycle) or Silica gel 60 F_{254} (Merck). ^{1}H, ^{13}C and 2D NMR spectroscopic data were recorded on 300 MHz Bruker FTNMR Ultra Shield spectrometers. ^{1}H NMR spectra are reported in ppm on the δ scale and referenced to the internal tetramethylsilane. The data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, m = multiplet, br = broad), coupling constant(s) in hertz (Hz), and integration. Infrared (IR) spectra were recorded on a Perkin Elmer 783 FTS165 FT-IR spectrometer. High-resolution mass spectra were obtained on a liquid chromatograph-mass spectrometer (2690, LCT, Waters, Micromass). The optical rotations were recorded on a JASCO P-1020 polarimeter. The circular dichroism (CD) spectra were recorded on a JASCO J-815 polarimeter. Melting points were measured using an Electrothermal IA9300 melting point apparatus and are uncorrected. Enantiopurity was determined using HPLC on an Agilent series 1200 equipped with a diode array UV detector using either CHIRALCEL® OD-H column (15 cm).

General procedure for hydrolytic kinetic resolution (HKR): To a flame-dried flask was added (*S*,*S*)- or (*R*,*R*)-cobalt(II) salen (0.005 equiv) and toluene (0.02 M). The reaction mixture was treated with AcOH (0.02 equiv) and stirred at room temperature open to air for 30 min over which time the color changed from orange-red to dark brown. The solution was

concentrated under reduced pressure to give a brown solid before the racemic epoxide **13** was added in one portion. The reaction was cooled to 0 °C and H_2O (0.60 equiv) was added dropwise and stirred at 0 °C to room temperature overnight. The reaction mixture was purified by column chromatography to afford (*R*)- or (*S*)-diol and (*S*)- or (*R*)-epoxide.

General procedure for methanolysis: To a solution of benzoate or acetate derivative (1.0 equiv) in MeOH (0.05 M) was added K_2CO_3 (3.0 equiv) and the reaction was stirred at rt until the starting benzoate or acetate derivative was completely consumed. The reaction mixture was concentrated under reduced pressure, diluted with H_2O and EtOAc. The aqueous phase was separated and further extracted with EtOAc (x3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography to give the corresponding alcohol derivative.

General procedure for TEMPO/PhI(OAc)$_2$-mediated oxidation: To a solution of alcohol (1.0 equiv) in CH_2Cl_2 (0.05 M) was added $PhI(OAc)_2$ (1.1 equiv), followed by TEMPO (33 mol%). The reaction mixture was stirred at rt overnight. The reaction mixture was then quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography to give aldehyde derivative.

General procedure for acetylide addition: To a solution of alkyne **11**[18] (1.3 equiv) in anhydrous THF (0.3 M) was added *n*-BuLi (*ca.* 1.5 M solution in hexane, 1.5 equiv) dropwise at –78 °C. After stirring for 1 h, a solution of aldehyde (1.0 equiv) in anhydrous THF (0.5 M) was slowly added. The reaction mixture was stirred from –78 °C to approximately 0 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (x3). The combined organic layer were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the propargylic alcohol derivative.

General procedure for acetylation: To a solution of alcohol (1.0 equiv) in CH_2Cl_2 (0.2 M) were added triethylamine (3.0 equiv), DMAP (0.3 equiv), followed by acetic anhydride (2.5 equiv). After stirring for 1 h at rt, the reaction was quenched with saturated aqueous NH_4Cl, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and

concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the acetate derivative.

General procedure for hydrogenation/hydrogenolysis: To a solution of benzyl ether derivative (1.0 equiv) in EtOH (0.03 M) was added Pd/C (5 wt%, 20 mol %). The reaction mixture was stirred at rt under H_2 atmosphere until the starting material was completely consumed, then filtered through a pad of Celite, washed with EtOAc and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the alcohol derivative.

General procedure for elimination: To a solution of iodide derivative (1.0 equiv) in THF (0.2 M) at 0 °C was added KO*t*-Bu (3.5 equiv). The reaction mixture was stirred from 0 °C to rt for 3 h, then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the terminal alkene derivative.

General procedure for desilylation: To a solution of silyl ether derivative (1.0 equiv) in dry THF (0.25 M) was added TBAF (1.0 M solution in THF, 3.0 equiv) dropwise at 0 °C. The reaction mixture was stirred from 0 °C to rt overnight. H_2O was then added and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the alcohol derivative.

General procedure for Pinnick oxidation: To a solution of aldehyde derivative (1.0 equiv) in *tert*-butyl alcohol (0.10 M) at 0 °C was added 2-methyl-2-butene (10.0 equiv), followed by a solution of sodium phosphate monobasic (6.0 equiv) and sodium chlorite (2.0 equiv) in H_2O (0.30 M). After being stirred at rt for 1 h, the reaction mixture was quenched with 1 M HCl and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the benzoic acid derivative**.**

General procedure for Mitsunobu esterification: To a solution of benzoic acid (1.0 equiv) and alcohol (1.0 equiv) in toluene (0.1 M) were added PPh_3 (2.0 equiv) and diisopropyl azodicarboxylate (DIAD) (2.0 equiv). The reaction mixture was stirred at rt for 2 h, then

diluted with EtOAc, quenched with H_2O and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the ester derivative.

General procedure for ring-closing metathesis: To a solution of diene (1.0 equiv) in CH_2Cl_2 (2.0 mM) was added 2nd generation Grubbs catalyst (10 mol %) and purged with argon at room temperature. The reaction mixture was heated at reflux until the diene precursor was completely consumed. The reaction was cooled to room temperature and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the desired macrolactone.

General procedure for Dess-Martin periodinane (DMP) oxidation: To a solution of alcohol derivative (1.0 equiv) in CH_2Cl_2 (0.03 M) was added Dess-Martin periodinane (DMP) (2.5 equiv). The reaction mixture was stirred at rt for 5 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the ketone derivative.

General procedure for deprotection of alkoxy ether group: To a solution of **39** or **50** (1.0 equiv) in MeOH (0.02 M) was treated with concentrated HCl (180.0 equiv) at 0 °C. The reaction was stirred from 0 °C to rt for 4 h, then neutralized with saturated $NaHCO_3$ and extracted with EtOAc (x3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography yielded the final product derivative.

(*R*)-6-(Benzyloxy)hexane-1,2-diol (14): (*R*)-Diol **14** was prepared from racemic epoxide **13** (5.21 g, 25.30 mmol) and (*S*,*S*)-cobalt(II) salen (76.7 mg, 0.13 mmol, 0.5 mol %) using the general procedure for hydrolytic kinetic resolution (HKR). The crude product was purified by column chromatography (20% EtOAc/hexanes–100% EtOAc) to afford diol **14** as a light yellow oil (2.49 g, 45%, 88% ee): R_f = 0.15 (50% EtOAc/hexanes); $[\alpha]_D^{28}$ = +4.90 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 4.48 (s, 2H), 3.67–3.60 (m, 1H), 3.55 (dd, *J* = 11.1, 2.4 Hz, 1H), 3.47 (t, *J* = 6.3 Hz, 2H), 3.36 (dd, *J* = 11.1, 7.8 Hz, 1H), 1.67–1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.36, 128.40, 127.74, 127.62, 72.93, 72.08, 70.24, 66.63, 32.77, 29.58, 22.26; IR (thin film) 3377, 2937, 2863, 1453,1097, 736

cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{20}NaO_3$ $(M + Na)^+$ 247.1310, found 247.1310; The enantiomeric excess was determined by HPLC analysis using CHIRALCEL® OD-H column eluting with 95:5 isopropanol/hexane (flow rate = 1.0 mL/min, pressure = 33.45 bar, temp = 26-28 °C): retention time = 16.602 min, retention time of (*S*)-enantiomer = 20.634 min.

(*R*)-6-(Benzyloxy)-2-(methoxymethoxy)hexan-1-ol (15): Alcohol **15** was prepared from benzoate **14b** (2.58 g, 6.93 mmol) using the general procedure for methanolysis. The crude residue was purified by column chromatography (20–40% EtOAc/hexanes) to give alcohol **15** (1.78 g, 98%, 73% over 3 steps from (*R*)-diol **14**) as a colorless oil: R_f = 0.23 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ = –31.98 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.14 (m, 5H), 4.62 (d, *J* = 6.6 Hz, 1H), 4.55 (d, *J* = 6.6 Hz, 1H), 4.38 (s, 2H), 3.51–41 (m, 3H), 3.37 (t, *J* = 6.6 Hz, 2H), 3.28 (s, 3H), 1.56–1.28 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.56, 128.25, 127.52, 127.41, 96.39, 80.34, 72.71, 70.04, 64.93, 55.33, 31.34, 29.67, 22.09; IR (thin film) 3444, 2939, 1454, 1362, 1098, 1036 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{24}NaO_4$ $(M + Na)^+$ 291.1572, found 291.1571.

(*R*)-6-(Benzyloxy)-2-(methoxymethoxy)hexanal (10): Aldehyde **10** was prepared from alcohol **15** (1.53 g, 5.71 mmol) using the general procedure for TEMPO/$PhI(OAc)_2$-mediated oxidation. Purification of the crude residue by column chromatography (10–40% EtOAc/hexanes) yielded aldehyde **10** as a light yellow oil (1.35 g, 87%): R_f = 0.39 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ = +14.87 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.8 Hz, 1H), 7.34–7.25 (m, 5H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.49 (s, 2H), 3.89 (td, *J* = 6.9, 1.8 Hz, 1H), 3.47 (t, *J* = 6.0 Hz, 2H), 3.40 (s, 3H), 1.73–1.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.82, 138.52, 128.37, 127.63, 127.55, 96.76, 82.31, 72.92, 69.91, 55.97, 29.78, 29.50, 21.67; IR (thin film) 2944, 1731, 1454, 1275, 1102, 918 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NaO_4$ $(M + Na)^+$ 289.1416, found. 289.1416.

(5*R*,10*R*)-5-(4-(Benzyloxy)butyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetradec-7-yn-6-ol (16): Propargylic alcohol **16** was prepared from alkyne **11** (2.04 g, 6.33 mmol) and aldehyde **10** (1.26 g, 4.70 mmol) using the general procedure for acetylide addition. The crude residue was purified by column chromatography (5–30% EtOAc/hexanes) to give propargylic alcohol **16** (1.77 g, 81% based on 270.3 mg of recovered aldehyde **10**) as a light yellow oil: R_f = 0.27 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ = +17.89 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.2 Hz, 4H), 7.42–7.24 (m, 11H), 4.72 (d,

J = 7.2 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.48 (s, 2H), 4.26–4.24 (m, 1H), 4.01–3.91 (m, 1H), 3.51–3.43 (m, 1H), 3.45 (t, *J* = 6.3 Hz, 2H), 3.39 (s, 3H), 2.45–2.26 (m, 2H), 1.78–1.37 (m, 6H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.60, 135.83, 134.23, 134.17, 134.12, 129.67, 128.38, 127.61, 97.68, 97.46, 84.77, 83.58, 83.25, 80.35, 79.79, 72.91, 70.23, 70.17, 68.29, 68.19, 65.38, 65.23, 55.91, 55.86, 31.42, 31.21, 29.77, 29.65, 29.44, 26.97, 22.97, 22.92, 22.55, 22.01, 19.22; IR (thin film) 3417, 2931, 2857, 1427, 1109, 1041 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{36}H_{48}NaO_5Si$ $(M + Na)^+$ 611.3169, found 611.3168.

(5*R*,10*R*)-5-(4-(Benzyloxy)butyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetradec-7-yn-6-yl acetate (17): Acetate **17** was prepared from propargylic alcohol **16** (1.40 g, 1.90 mmol) using the general procedure for acetylation. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give **17** (1.46 g, 97%) as a light yellow oil: R_f = 0.40 (20% EtOAc/hexanes); $[\alpha]_D^{28}$ = +20.88 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.40–7.23 (m, 11H), 5.55 (dt, *J* = 2.7, 1.8 Hz, 0.65H), 5.46 (dt, *J* = 5.7, 1.8 Hz, 0.37H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 4.48 (s, 2H), 4.02–3.91 (m, 1H), 3.71–3.59 (m, 1H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.35 (s, 3H), 2.42–2.26 (m, 2H), 2.06 (s, 3H), 1.73–1.37 (m, 6H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.91, 169.68, 138.60, 135.79, 134.19, 133.99, 129.67, 129.62, 128.34, 127.59, 127.49, 96.88, 96.17, 84.72, 84.37, 78.33, 78.01, 72.87, 70.19, 67.97, 66.20, 66.01, 55.86, 55.79, 30.80, 30.39, 29.77, 29.67, 29.36, 26.91, 22.89, 22.52, 21.83, 21.01, 19.19; IR (thin film) 2932, 2857, 1743, 1369, 1231, 1106 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{38}H_{50}NaO_6Si$ $(M + Na)^+$ 653.3274, found 653.3276.

(5*R*,10*R*)-5-(4-Hydroxybutyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetradecan-6-yl acetate (18): Alcohol **18** was prepared from compound **17** (1.36 g, 2.15 mmol) using the general procedure for hydrogenation/hydrogenolysis. The crude product was purified by column chromatography (20–40% EtOAc/hexanes) to afford alcohol **18** (916.9 mg, 75%) as a light yellow oil: R_f = 0.17 (30% EtOAc/hexanes); $[\alpha]_D^{28}$ = +7.88 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 4H), 7.41–7.34 (m, 6H), 5.03–4.91 (m, 1H), 4.70 (d, *J* = 7.2 Hz. 1H), 4.57 (d, *J* = 7.2 Hz, 1H), 3.82 (sext, *J* = 6.0 Hz, 1H), 3.66–3.49 (m, 3H), 3.37 (s, 3H), 2.03 (s, 3H), 1.58–1.20 (m, 12H), 1.04 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.79, 135.83, 134.76, 134.42, 129.46, 129.39, 127.47, 127.37, 96.55, 95.90, 78.32, 77.94, 74.90, 74.39, 69.43, 69.19, 62.51, 62.39, 55.84, 55.72, 39.39, 39.13,

32.58, 30.23, 30.09, 30.03, 29.23, 26.99, 23.26, 23.17, 21.93, 21.61, 21.53, 21.35, 21.09, 19.23; IR (thin film) 3451, 2933, 1737, 1373, 1243, 1110 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{48}NaO_6Si$ $(M + Na)^+$ 567.3118, found 567.3120.

(5*R*,10*R*)-5-(But-3-enyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetra decan-6-ol (19): Compound **19** was prepared from iodide **18a** (920.0 mg, 1.40 mmol) using general procedure for elimination. Purification of the crude residue by column chromatography (20% EtOAc/hexanes) afforded **19** (606.6 mg, 89%) as a light yellow oil: R_f = 0.56 (30% EtOAc/hexanes); $[\alpha]_D^{27}$ = +5.26 (*c* 0.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.41–7.33 (m, 6H), 5.87–5.75 (m, 1H), 5.03 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.98 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 6.9 Hz, 1H), 3.88–3.81(m, 1H), 3.52–3.45 (m, 2H), 3.40 (s, 3H), 2.23–1.99 (m, 2H), 1.74–1.26 (m, 8H), 1.08 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.24, 135.89, 134.91, 134.64, 129.45, 129.39, 127.47, 127.40, 114.96, 114.90, 97.31, 97.21, 83.23, 82.99, 72.94, 72.72, 69.59, 69.50, 55.81, 39.55, 39.46, 33.23, 31.80, 30.31, 30.08, 29.44, 29.29, 27.06, 23.22, 23.14, 21.94, 21.30, 19.26; IR (thin film) 3461, 2932, 1427, 1105, 1036, 702 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{44}NaO_4Si$ $(M + Na)^+$ 507.2907, found 507.2907.

(5*R*,10*R*)-5-(But-3-enyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetra decan-6-yl acetate (20): Compound **20** was prepared from **19** (606.6 mg, 1.25 mmol) using the general procedure for acetylation. Purification of the crude residue by column chromatography (10% EtOAc/hexanes) afforded **20** (652.6 mg, 98%) as a light yellow oil: R_f = 0.62 (30% EtOAc/hexanes); $[\alpha]_D^{27}$ = +10.0 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 4H), 7.44–7.34 (m, 6H), 5.88–5.73 (m, 1H), 5.08–5.06 (m, 1H), 5.02–4.93 (m, 2H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 6.9 Hz, 1H), 3.82 (sext, *J* = 6.0 Hz, 1H), 3.63–3.51 (m, 1H), 3.38 (s, 3H), 2.31–2.07 (m, 2H), 2.03 (s, 3H), 1.72–1.19 (m, 8H), 1.04 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.67, 170.43, 138.10, 135.85, 134.94, 134.85, 134.64, 134.50, 129.48, 129.40, 129.35, 127.49, 127.43, 127.35, 115.02, 114.86, 96.77, 96.10, 95.98, 77.88, 77.80, 77.68, 77.44, 77.36, 75.00, 74.87, 74.49, 74.38, 69.49, 69.29, 69.23, 55.77, 55.67, 39.45, 39.24, 29.99, 29.92, 29.82, 29.53, 27.03, 23.28, 23.18, 23.09, 21.56, 21.33, 21.09, 20.94, 19.26, 19.23; IR (thin film) 2932, 2858, 1737, 1374, 1240, 1105 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{46}NaO_5Si$ $(M + Na)^+$ 549.3012, found 549.3012.

(5*R*,10*R*)-10-Hydroxy-5-(methoxymethoxy)undec-1-en-6-yl acetate (9): Alcohol **9** was prepared from compound **20** (656.2 mg, 1.24 mmol) using the general procedure for desilylation. The crude residue was purified by column chromatography (10–30% EtOAc/hexanes) to give alcohol **9** (298.2 mg, 83%) as a colorless oil: R_f = 0.22 (30% EtOAc/hexanes); $[\alpha]_D^{27}$ = +4.35 (*c* 0.23, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88–5.73 (m, 1H), 5.08–4.97 (m, 3H), 4.72 (d, *J* = 7.2 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 3.78–3.74 (m, 1H), 3.67–3.56 (m, 1H), 3.39 (s, 3H), 2.36–2.13 (m, 2H), 2.07 (s, 3H), 1.71–1.32 (m, 8H), 1.17 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.88, 170.77, 137.97, 137.93, 115.01, 114.97, 96.64, 95.94, 77.72, 77.51, 74.81, 74.25, 67.54, 55.84, 55.72, 38.85, 29.80, 29.76, 29.66, 29.62, 29.49, 29.28, 23.38, 21.86, 21.70, 21.08, 21.03 ;IR (thin film) 3447, 2934, 1736, 1374, 1242, 1097 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}NaO_5$ $(M + Na)^+$ 311.1834, found 311.1834.

Methyl 2-(3,5-bis(ethoxymethoxy)-2-formylphenyl)acetate (31): To a solution of phenol **30** (2.20 g, 10.47 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added DMAP (383.6 mg, 31.40 mmol, 0.3 equiv) and EtN(*i*-Pr)$_2$ (11 mL, 62.82 mmol, 6.0 equiv), followed by chloromethyl ethyl ether (EOMCl) (3.1 mL, 33.50 mmol, 3.2 equiv) dropwise. The reaction was stirred from 0 °C to rt overnight before saturated aqueous NH_4Cl (70 mL) was added and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude residue by column chromatography (5–20% EtOAc/hexanes) yielded **31** (2.87 g, 84%) as a yellow solid: R_f = 0.46 (40% EtOAc/hexanes); mp 81–83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.45 (s, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.53 (d, *J* = 2.1 Hz, 1H), 5.31 (s, 2H), 5.26 (s, 2H), 3.93 (s, 2H), 3.79–3.69 (m, 4H), 3.71 (s, 3H), 1.27–1.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.21, 171.53, 163.27, 162.44, 138.70, 118.15, 113.37, 101.86, 93.60, 92.85, 64.88, 64.74, 51.86, 40.43, 15.04; IR (thin film) 2978, 1740, 1677, 1602, 1285, 1149 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}NaO_7$ $(M + Na)^+$ 349.1263, found 349.1263.

2-(3,5-Bis(ethoxymethoxy)-2-(hydroxymethyl)phenyl)ethanol (32): To a solution of ester **31** (2.79 g, 8.47 mmol) in MeOH (21 mL) and THF (21 mL) at 0 °C were added $NaBH_4$ (966.4 mg, 25.41 mmol, 3.0 equiv). The reaction was stirred from 0 °C to rt overnight before saturated aqueous NH_4Cl (70 mL) was added and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over with anhydrous Na_2SO_4 and concentrated *in vacuo* to give diol **32** (2.66 g, quant.) as a light yellow oil, which was used

for the next step without further purification: R_f = 0.07 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (d, *J* = 2.4 Hz, 1H), 6.57 (d, *J* = 2.1 Hz, 1H), 5.22 (s, 2H), 5.18 (s, 2H), 4.64 (s, 2H), 3.79 (t, *J* = 6.0 Hz, 2H), 3.76–3.67 (m, 4H), 2.88 (t, *J* = 6.3 Hz, 2H), 1.21 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.89, 156.86, 141.03, 122.89, 110.70, 102.28, 93.94, 93.10, 64.51, 64.24, 63.27, 55.15, 35.87, 15.05; IR (thin film) 3347, 2975, 2896, 1605, 1281, 1144 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{24}NaO_6$ $(M + Na)^+$ 323.1471, found 323.1471.

2-((*tert*-Butyldimethylsilyloxy)methyl)-3,5-bis(ethoxymethoxy)phenethyl 4-methylbenzenesulfonate (33): To a solution of diol **32** (608.2 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (390 µL, 2.80 mmol, 1.4 equiv) and DMAP (73.7 mg, 0.60 mmol, 0.3 equiv). The reaction was cooled to 0 °C, added TsCl (533.9 mg, 2.80 mmol, 1.4 equiv) and stirred from 0 °C to rt for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl (25 mL) and extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give the desired monotosylate (340.5 mg, 37%) as a light yellow oil, which was immediately used in the next step: R_f = 0.23 (40% EtOAc/hexanes).

To a solution of the monotosylate (180.6 mg, 0.40 mmol) in CH_2Cl_2 (3 mL) at 0 °C were added imidazole (54.2 mg, 0.80 mmol, 2 equiv), DMAP (14.6 mg, 0.12 mmol, 0.3 equiv), followed by TBSCl (90.4 mg, 0.60 mmol, 1.5 equiv). After stirring at rt for 1 h, it was quenched with H_2O (5 mL) and extracted with EtOAc (3x5 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (5–20% EtOAc/hexanes) to give **33** (160.9 mg, 71%) as a colorless oil: R_f = 0.58 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 5.18 (s, 2H), 5.15 (s, 2H), 4.64 (s, 2H), 4.24 (t, *J* = 7.5 Hz, 2H), 3.71 (q, *J* = 6.9 Hz, 2H), 3.70 (q, *J* = 6.9 Hz, 2H), 3.05 (t, *J* = 7.5 Hz, 2H), 2.42 (s, 3H), 1.22 (t, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 6.9 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.63, 156.54, 144.49, 138.36, 133.24, 129.75, 127.82, 122.02, 111.00, 102.34, 93.66, 93.15, 70.92, 64.32, 64.26, 55.91, 32.69, 25.97, 21.59, 18.36, 15.08, -5.34; IR (thin film) 2956, 2895, 1605, 1360, 1176, 1062 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{44}NaO_8SSi$ $(M + Na)^+$ 591.2424, found 591.2424.

(2,4-Bis(ethoxymethoxy)-6-vinylbenzyloxy)(tert-butyl)dimethylsilane (34): Alkene **34** was prepared from tosylate **33** (85.2 mg, 0.15 mmol) using the general procedure for elimination. The crude residue was purified by column chromatography (10% EtOAc/hexanes) to give **34** (50.6 mg, 85%) as colorless oil: R_f = 0.65 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 2.4 Hz, 1H), 5.69 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.34 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.24 (s, 4H), 4.77 (s, 2H), 3.76 (q, *J* = 7.2 Hz, 2H), 3.75 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 6H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.67, 156.39, 140.34, 134.88, 121.03, 116.24, 106.67, 103.11, 93.73, 93.22, 64.28, 64.19, 55.96, 25.98, 18.45, 15.10, -5.23; IR (thin film) 2930, 1601, 1579, 1471, 1254, 1148 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{36}NaO_5Si$ $(M + Na)^+$ 419.2230, found 419.2231.

(2,4-Bis(ethoxymethoxy)-6-vinylphenyl)methanol (35): To a solution of silyl ether **34** (160.6 mg, 0.40 mmol) in THF (4 mL) at 0 °C was added TBAF (1.0 M solution in THF, 1.6 mL, 1.6 equiv). The reaction mixture was stirred from 0 °C to room temperature for 1 h before it was heated at 60 °C for 1.5 h. The reaction was then cooled to room temperature, then quenched with H_2O (5 mL) and extracted with EtOAc (3x5 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (10–30% EtOAc/hexanes) to give alcohol **35** (106.5 mg, 93%) as a colorless oil: R_f = 0.38 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 5.67 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.36 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.23 (d, *J* = 1.8 Hz, 2H), 5.21 (d, *J* = 1.8 Hz, 2H), 4.71 (s, 2H), 3.73 (q, *J* = 7.2 Hz, 2H), 3.72 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.86, 156.92, 139.57, 134.11, 121.29, 117.42, 107.09, 103.37, 93.97, 93.13, 64.64, 64.25, 56.04, 15.07, 15.04; IR (thin film) 3444, 2977, 1601, 1578, 1283, 1146 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NaO_5$ $(M + Na)^+$ 305.1365, found 305.1365.

2,4-Bis(ethoxymethoxy)-6-vinylbenzaldehyde (36): To a solution of alcohol **35** (106.5 mg, 0.38 mmol) in DMSO (4.3 mL) and toluene (4.3 mL) were added IBX (376.2 mg, 1.33 mmol, 3.5 equiv). The reaction mixture was stirred at rt for 2 h before being quenched with H_2O (4 mL), filtered and extracted with EtOAc (3x5 mL). The combined organic layers were washed with brine, dried over with anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (5–20% EtOAc/hexanes) to give aldehyde **36** (101.2

mg, 96%) as a light yellow oil: R_f = 0.57 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.50 (s, 1H), 7.56 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.84 (s, 2H), 5.63 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.37 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.31 (s, 2H), 5.28 (s, 2H), 3.76 (q, *J* = 7.2 Hz, 2H), 3.75 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.55, 162.54, 162.29, 143.00, 136.02, 117.44, 108.10, 102.08, 102.03, 93.63, 92.84, 64.88, 64.68, 15.05; IR (thin film) 2977, 1678, 1594, 1277, 1149, 1026 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NaO_5$ $(M + Na)^+$ 303.1208, found 303.1209.

2,4-Bis(ethoxymethoxy)-6-vinylbenzoic acid (8b): Benzoic acid **8b** was prepared from aldehyde **36** (101.2 mg, 0.36 mmol) using the general procedure for Pinnick oxidation. The crude residue was purified by column chromatography (20–40% EtOAc/hexanes) to give benzoic acid **8b** (86.6 mg, 81%) as a light yellow oil: R_f = 0.18 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 17.4, 11.1 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 2.1 Hz, 1H), 5.71 (d, *J* = 17.4 Hz, 1H), 5.36 (d, *J* = 11.1 Hz, 1H), 5.28 (s, 2H), 5.26 (s, 2H), 3.75 (qn, *J* = 7.2 Hz, 4H), 1.23 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.28, 159.68, 156.25, 139.53, 134.38, 117.23, 115.61, 107.01, 103.31, 94.02, 93.00, 64.80, 64.49, 15.04, 14.98; IR (thin film) 2978, 1709, 1599, 1285, 1153, 1027 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}NaO_6$ $(M + Na)^+$ 319.1158, found 319.1159.

(2*S*,7*R*)-6-Acetoxy-7-(methoxymethoxy)undec-10-en-2-yl 2,4-bis(ethoxymethoxy)-6-vinylbenzoate (7b): Ester **7b** was prepared from alcohol **9** (98.4 mg, 0.34 mmol) and benzoic acid **8b** (108.1 mg, 0.36 mmol) using the general procedure for Mitsunobu esterification. The crude residue was purified by column chromatography (10–20% EtOAc/hexanes) to give ester **7b** (135.6 mg, 70%) as a light yellow oil: R_f = 0.63 (50% EtOAc/hexanes); $[\alpha]_D^{27}$ = +5.00 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, *J* = 2.1 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.69 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.88–5.77 (m, 1H), 5.71 (d, *J* = 17.4 Hz, 1H), 5.33 (d, *J* = 10.8 Hz, 1H), 5.22 (s, 2H), 5.20 (s, 2H), 5.19–5.11 (m, 1H), 5.08–4.97 (m, 3H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 3.71 (qd, *J* = 6.9, 1.8 Hz, 4H), 3.66–3.55 (m, 1H), 3.39 (s, 3H), 2.31–2.10 (m, 2H), 2.06 (s, 3H), 1.71–1.36 (m, 8H), 1.33 (d, *J* = 6.3 Hz, 3H), 1.22 (t, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.71, 170.55, 167.39, 158.86, 155.27, 137.98, 137.15, 133.38, 118.12, 117.17, 115.10, 115.04, 105.65, 103.09, 96.65, 96.02, 93.35, 93.06, 77.68, 77.50, 74.74, 74.06, 71.65, 64.39, 64.29, 55.90, 55.79, 35.73, 29.91, 29.87, 29.55, 29.05, 21.75, 21.57, 21.13, 21.07, 19.99, 15.07,

15.03; IR (thin film) 2976, 2934, 1732, 1601, 1265, 1151 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{46}NaO_{10}$ $(M + Na)^+$ 589.2989, found 589.2988.

Macrolactones 37: Macrolactones **37** were prepared from ester **7b** (80.2 mg, 0.10 mmol) using the general procedure for ring-closing metathesis. The crude residue was purified by column chromatography (10–20% EtOAc/hexanes) to give macrolactones **37** as a mixture of diastereomers.

Major diastereomer of 37. colorless oil (42.5 mg, 56%); R_f = 0.53 (50% EtOAc/hexanes); $[\alpha]_D^{28}$ = +100.02 (*c* 0.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, *J* = 1.8 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H), 6.38–6.34 (m, 2H), 5.22 (s, 4H), 5.20–5.05 (m, 2H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.54 (d, *J* = 6.9 Hz, 1H), 3.76–3.67 (m, 5H), 3.37 (s, 3H), 2.39–2.35 (m, 2H), 2.07 (s, 3H), 2.00–1.46 (m, 8H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.25–1.19 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.76, 168.23, 158.67, 154.76, 135.86, 132.48, 125.66, 118.36, 105.17, 102.22, 95.77, 93.23, 93.09, 75.39, 75.00, 69.34, 64.41, 64.30, 55.72, 34.92, 29.69, 29.37, 25.89, 25.52, 21.23, 20.60, 20.47, 15.09, 15.01; IR (thin film) 2932, 1730, 1601, 1239, 1149, 1021 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{42}NaO_{10}$ $(M + Na)^+$ 561.2676, found 561.2676.

Minor diastereomer of 37. colorless oil (24.0 mg, 31%); R_f = 0.48 (50% EtOAc/hexanes); $[\alpha]_D^{28}$ = +110.02 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J* = 1.8 Hz, 1H), 6.76 (d, *J* = 1.8 Hz, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.09 (ddd, *J* = 15.9, 9.3, 5.1 Hz, 1H), 5.47–5.37 (m, 1H), 5.22 (s, 4H), 4.97 (dt, *J* = 9.6, 2.7 Hz, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.76–3.67 (m, 5H), 3.37 (s, 3H), 2.42–2.13 (m, 2H), 2.09 (s, 3H), 2.00–1.33 (m, 8H), 1.28–1.19 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.52, 167.38, 158.81, 154.82, 136.64, 132.73, 128.03, 118.16, 105.81, 102.51, 96.54, 93.31, 93.09, 74.44, 71.98, 70.14, 64.37, 64.32, 55.77, 34.05, 29.67, 29.15, 28.75, 28.11, 21.19, 18.82, 17.76, 15.07, 15.00; IR (thin film) 2944, 1728, 1601, 1246, 1151, 1104 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{42}NaO_{10}$ $(M + Na)^+$ 561.2676, found 561.2676.

Major diastereomer of alcohol 38: The major diastereomer of alcohol **38** was prepared from the major diastereomer of macrolactone acetate **37** (42.5 mg, 0.08 mmol) using the general procedure for methanolysis. The crude residue was purified by column chromatography (20–40% EtOAc/hexanes) to give the major diastereomer of alcohol **38** (30.2 mg, 76%) as a colorless oil: R_f = 0.23 (50% EtOAc/hexanes); $[\alpha]_D^{28}$ = +90.02 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, *J* = 1.8 Hz, 1H), 6.73 (d, *J* = 1.8 Hz, 1H),

6.33 (s, 2H), 5.22–5.16 (m, 5H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 3.88–3.84 (m, 1H), 3.71 (qd, *J* = 6.9, 4.2 Hz, 4H), 3.65–3.61 (m, 1H), 3.40 (s, 3H), 2.44–2.25 (m, 2H), 1.90–1.36 (m, 8H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.13, 158.68, 154.82, 136.09, 132.79, 126.03, 118.50, 105.53, 102.34, 96.03, 93.33, 93.16, 78.42, 73.30, 69.91, 64.43, 64.33, 55.76, 35.12, 31.23, 29.70, 26.04, 24.41, 20.50, 20.27, 15.10, 15.02; IR (thin film) 3468, 2933, 1725, 1599, 1262, 1149 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}NaO_9$ $(M + Na)^+$ 519.2570, found 519.2570.

Minor diastereomer of alcohol 38: The minor diastereomer of alcohol **38** was prepared from the minor diastereomer of macrolactone acetate **37** (24.0 mg, 0.044 mmol) using the general procedure for methanolysis. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give the minor diastereomer of alcohol **38** (15.3 mg, 70%) as a light yellow oil: R_f = 0.32 (50% EtOAc/hexanes); $[\alpha]_D^{28}$ = + 52.64 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J* = 1.5 Hz, 1H), 6.76 (d, *J* = 1.5 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.15 (ddd, *J* = 15.9, 8.4, 4.8 Hz, 1H), 5.36–5.31 (m, 1H), 5.23 (s, 4H), 4.65 (s, 2H), 3.76–3.67 (m, 4H), 3.61–3.58 (m, 1H), 3.52–3.46 (m, 1H), 3.39 (s, 3H), 2.45–2.16 (m, 2H), 1.98–1.53 (m, 8H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.25–1.19 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.86, 158.92, 154.93, 136.61, 132.86, 127.80, 118.34, 105.68, 102.55, 97.14, 93.38, 93.20, 78.51, 70.97, 70.50, 64.52, 64.46, 55.97, 35.13, 32.76, 29.33, 28.06, 19.77, 18.92, 15.22, 15.14; IR (thin film) 3483, 2932, 1722, 1601, 1262, 1150 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}NaO_9$ $(M + Na)^+$ 519.2570, found 519.2570.

(3*S*,8*R*,*E*)-14,16-Bis(ethoxymethoxy)-8-(methoxymethoxy)-3-methyl-3,4,5,6,9,10-hexa hydro-1H-benzo[c][1]oxacyclotetradecine-1,7(8H)-dione (39): Ketone **39** was prepared from the major diastereomer of alcohol **38** (30.2 mg, 0.061 mmol) and the minor diastereomer of alcohol **38** (15.3 mg, 0.031 mmol) using the general procedure for DMP oxidation. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give ketone **39** (26.5 mg, 83% from the major diastereomer of **38** and 12.4 mg, 81% from the minor diastereomer of **38**) as a colorless oil: R_f = 0.48 (50% EtOAc/hexanes); $[\alpha]_D^{28}$ = +60.01 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J* = 1.8 Hz, 1H), 6.76 (d, *J* = 1.8 Hz, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.82 (d, *J* = 2.1 Hz, 1H), 6.17 (ddd, *J* = 15.9, 7.8, 5.1 Hz, 1H), 5.23–5.16 (m, 5H), 4.63 (d, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 6.9 Hz, 1H), 4.21 (t, *J* = 6.0 Hz, 1H), 3.76–3.68 (m, 4H), 3.32 (s, 3H), 2.55–1.61 (m, 10H), 1.36 (d, *J* = 6.0 Hz, 3H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.22 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.54,

167.90, 158.87, 154.91, 136.15, 132.42, 127.79, 118.16, 105.49, 102.52, 96.25, 93.31, 93.08, 78.23, 70.88, 64.43, 64.34, 55.80, 40.88, 34.75, 29.57, 27.33, 20.98, 20.66, 15.07, 14.99; IR (thin film) 2974, 2930, 1724, 1599, 1262, 1150 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{38}NaO_9$ $(M + Na)^+$ 517.2414, found 517.2415.

5'-Hydroxyzearalenone (5): 5'-Hydroxyzearalenone (**5**) was prepared from ketone **39** (31.2 mg, 0.063 mmol) using the general procedure for deprotection of alkoxy ether group. The crude residue was purified by column chromatography (20–40% EtOAc/hexanes) to give 5'-hydroxyzearalenone (**5**) (13.1 mg, 62%) as a white solid: R_f = 0.25 (50% EtOAc/hexanes); mp 173–175 °C; $[\alpha]_D^{28}$ = −25.98 (*c* 0.15, acetone); CD (c 1.72x10^{-3} M, MeOH) λ_{max}(mdeg): 266 nm (–21.73); ^{1}H NMR (300 MHz, acetone-d_6) δ 11.13 (s, 1H), 9.10 (brs, 1H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.25 (d, *J* = 2.4 Hz, 1H), 6.02 (ddd, *J* = 15.6, 6.9, 6.6 Hz, 1H), 5.11–5.01 (m, 1H), 4.24 (q, *J* = 5.1 Hz, 1H), 4.15 (d, *J* = 5.1 Hz, 1H), 2.77–2.69 (m, 1H), 2.48–2.36 (m, 1H), 2.33–2.23 (m, 1H), 2.19–2.05 (m, 1H), 1.94–1.72 (m, 6H), 1.34 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 213.03, 171.66, 164.57, 162.67, 143.32, 132.32, 131.31, 108.20, 105.56, 102.35, 76.03, 74.26, 38.77, 35.18, 32.27, 28.79, 21.10, 19.88; IR (thin film) 3279, 2931, 1702, 1648, 1610, 1259 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NaO_6$ $(M + Na)^+$ 357.1314, found 357.1314.

(*S*)-6-(Benzyloxy)hexane-1,2-diol (40): (*S*)-diol **40** was prepared from racemic epoxide **13** (8.10 g, 39.3 mmol) and (*R*,*R*)-cobalt(II) salen (126.4 mg, 0.21 mmol) using general procedure for hydrolytic kinetic resolution (HKR). Purification of the crude residue by column chromatography (20% EtOAc/hexanes–100% EtOAc) gave diol **40** as a light yellow oil (3.95 g, 45%, 94% ee): R_f = 0.17 (50% EtOAc/hexanes); $[\alpha]_D^{28}$ = −4.76 (*c* 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.48 (s, 2H), 3.6–3.64 (m, 1H), 3.57 (dd, *J* = 11.1, 2.4 Hz, 1H), 3.47 (t, *J* = 6.0 Hz, 2H), 3.38 (dd, *J* = 11.1, 7.5 Hz, 1H), 1.71–1.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.35, 128.41, 127.75, 127.63, 72.93, 72.08, 70.25, 66.61, 32.77, 29.59, 22.27; IR (thin film) 3378, 2937, 2863, 1453, 1098, 736 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{20}NaO_3$ $(M + Na)^+$ 247.1310, found 247.1310. The enantiomeric excess was determined by HPLC analysis using CHIRALCEL® OD-H column eluting with 95:5 isopropanol/hexane (flow rate = 1.0 mL/min, pressure = 32.48 bar, temp = 27-29 °C): retention time = 20.859 min, retention time of (*R*)-enantiomer = 17.617 min.

(*S*)-6-(Benzyloxy)-2-(methoxymethoxy)hexan-1-ol (41): Alcohol **41** was prepared from compound **40b** (4.28 g, 11.5 mmol) using the general procedure for methanolysis. The crude residue was purified by column chromatography (20–40% EtOAc/hexanes) to give alcohol **41** (2.96 g, 96%, 72% over 3 steps from (*S*)-diol **40**) as a colorless oil: R_f = 0.20 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ = +33.67 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.25 (m, 5H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.65 (d, *J* = 6.9 Hz, 1H), 4.47 (s, 2H), 3.53–3.49 (m, 2H), 3.45 (t, *J* = 6.3 Hz, 2H), 3.39 (s, 3H), 1.63–1.42 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.58, 128.34, 127.61, 127.51, 96.85, 81.68, 72.88, 70.11, 65.48, 55.57, 31.45, 29.73, 22.23; IR (thin film) 3448, 2940, 1454, 1110, 1037, 917 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{24}NaO_4$ $(M + Na)^+$ 291.1572, found 291.1572.

(*S*)-6-(Benzyloxy)-2-(methoxymethoxy)hexanal (*epi*-10): Aldehyde *epi*-**10** was prepared from alcohol **41** (1.32 g, 4.92 mmol) using the general procedure for TEMPO/$PhI(OAc)_2$-mediated oxidation. Purification of the crude residue by column chromatography (10–40% EtOAc/hexanes) yielded aldehyde *epi*-**10** (1.22 g, 93%) as a light yellow oil: R_f = 0.41 (30% EtOAc/hexanes); $[\alpha]_D^{25}$ = –14.74 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.8 Hz, 1H), 7.34–7.24 (m, 5H), 4.72 (d, *J* = 6.9 Hz, 2H), 4.68 (d, *J* = 6.9 Hz, 2H), 4.49 (s, 2H), 3.89 (td, *J* = 7.2, 1.8 Hz, 1H), 3.47 (t, *J* = 6.0 Hz, 2H), 3.40 (s, 3H), 1.73–1.46 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.83, 138.52, 128.37, 127.63, 127.55, 96.76, 82.31, 72.92, 69.91, 55.97, 29.78, 29.50, 21.68; IR (thin film) 2942, 1733, 1454, 1101, 1041, 918 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}NaO_4$ $(M + Na)^+$ 289.1416, found 289.1416.

(5*S*,10*R*)-5-(4-(Benzyloxy)butyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetradec-7-yn-6-ol (42): Propargylic alcohol **42** was prepared from alkyne **11** (1.79 g, 5.56 mmol) and aldehyde *epi*-**10** (1.13 g, 4.28 mmol) using the general procedure for acetylide addition. The crude residue was purified by column chromatography (5–30% EtOAc/hexanes) to give propargylic alcohol **42** (1.62 g, 83% based on 250.1 mg of recovered aldehyde *epi*-**10**) as a light yellow oil: R_f = 0.27 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ = +16.86 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4H), 7.41–7.23 (m, 11H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.64 (d, *J* = 6.9 Hz, 1H), 4.48 (s, 2H), 4.25–4.22 (m, 1H), 4.01–3.89 (m, 1H), 3.51–3.43 (m, 3H), 3.40 (s, 3H), 2.45–2.26 (m, 2H), 1.80–1.34 (m, 6H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.62, 135.82, 134.22, 134.16, 129.64, 128.36, 127.60, 97.65, 97.46, 84.63, 83.56, 83.22, 80.38, 79.77, 72.89, 70.22, 70.17, 68.29,

68.20, 65.37, 65.23, 55.90, 55.84, 31.38, 31.21, 29.76, 29.65, 29.43, 26.96, 22.97, 22.90, 22.52, 21.99, 19.20; IR (thin film) 3410, 2931, 2858, 1427, 1110, 1042 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{36}H_{48}NaO_5Si$ $(M + Na)^+$ 611.3169, found 611.3169.

(5*S*,10*R*)-5-(4-(Benzyloxy)butyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetradec-7-yn-6-yl acetate (43): Acetate **43** was prepared from propargylic alcohol **42** (965.8 mg, 1.64 mmol) using the general procedure for acetylation. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give **43** (1.01 g, 97%) as a light yellow oil: R_f = 0.41 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ = –3.84 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.44–7.23 (m, 11H), 5.55 (d, *J* = 1.8 Hz, 0.66H), 5.44 (dt, *J* = 6.0, 1.8 Hz, 0.34H), 4.74 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 4.48 (s, 2H), 3.95 (sext, *J* = 6.0 Hz, 1H), 3.71–3.60 (m, 1H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.36 (s, 3H), 2.42–2.26 (m, 2H), 2.07 (s, 3H), 1.73–1.38 (m, 6H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.97, 169.70, 138.62, 135.81, 134.22, 134.02, 129.69, 129.64, 128.37, 127.62, 127.58, 127.52, 96.91, 96.18, 84.70, 84.43, 78.33, 78.02, 72.90, 70.21, 67.96, 66.22, 66.03, 55.90, 55.83, 30.81, 30.40, 29.78, 29.69, 29.36, 26.92, 22.90, 22.53, 21.85, 21.04, 19.20; IR (thin film) 2932, 2857, 1743, 1599, 1427, 1232 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{38}H_{50}NaO_6Si$ $(M + Na)^+$ 653.3274, found 653.3276.

(5*S*,10*R*)-5-(4-Hydroxybutyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetradecan-6-yl acetate (44): Alcohol **44** was prepared from compound **43** (980 mg, 1.55 mmol) using the general procedure for hydrogenation/hydrogenolysis. The crude product was purified by column chromatography (20–40% EtOAc/hexanes) to afford alcohol **44** (560.1 mg, 66%) as a light yellow oil: R_f = 0.17 (30% EtOAc/hexanes); $[\alpha]_D^{27}$ = +4.97 (*c* 1.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.6 Hz, 4H), 7.44–7.33 (m, 6H), 5.02–4.91 (m, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* = 6.9 Hz, 1H), 3.88–3.76 (m, 1H), 3.66–3.50 (m, 3H), 3.37 (s, 3H), 2.02 (s, 3H), 1.59–1.19 (m, 12H), 1.05 (s, 9H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.82, 170.77, 135.87, 134.81, 134.44, 129.49, 129.42, 127.51, 127.41, 96.59, 95.95, 78.25, 77.95, 74.97, 74.40, 69.42, 69.20, 62.65, 62.51, 55.89, 55.77, 39.37, 39.19, 32.63, 30.29, 30.09, 29.96, 29.28, 27.03, 23.32, 23.13, 21.96, 21.77, 21.55, 21.13, 19.28; IR (thin film) 3446, 2932, 1736, 1379, 1242, 1109 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{48}NaO_6Si$ $(M + Na)^+$ 567.3118, found 567.3118.

(5*S*,10*R*)-5-(But-3-enyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetra decan-6-ol (45): Alkene **45** was prepared from iodide **44a** (531.9 mg, 0.81 mmol) using general procedure for elimination. Purification of the crude residue by column chromatography (20% EtOAc/hexanes) afforded **45** (380.0 mg, 96%) as a light yellow oil: R_f = 0.51 (30% EtOAc/hexanes); $[\alpha]_D^{27}$ = +7.50 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.43–7.32 (m, 6H), 5.87–5.73 (m, 1H), 5.06–4.96 (m, 2H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 6.9 Hz, 1H), 3.90–3.81 (m, 1H), 3.56–3.45 (m, 2H), 3.39 (s, 3H), 2.30–1.99 (m, 2H), 1.71–1.26 (m, 6H), 1.08 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.24, 135.89, 134.90, 134.64, 129.45, 129.39, 127.47, 127.40, 114.96, 114.90, 97.23, 83.30, 82.71, 72.94, 72.68, 69.54, 69.40, 55.82, 55.79, 39.49, 39.40, 33.27, 31.65, 30.26, 30.09, 29.46, 29.32, 27.06, 23.17, 23.12, 21.75, 21.25, 19.26; IR (thin film) 3463, 2932, 1427, 1105, 1036, 703 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{29}H_{44}NaO_4Si$ $(M + Na)^+$ 507.2907, found 507.2907.

(5*S*,10*R*)-5-(But-3-enyl)-10,13,13-trimethyl-12,12-diphenyl-2,4,11-trioxa-12-silatetra decan-6-yl acetate (46): Acetate **46** was prepared from alcohol **45** (330.2 mg, 0.68 mmol) using the general procedure for acetylation. Purification of the crude residue by column chromatography (10% EtOAc/hexanes) afforded **46** (349.6 mg, 97%) as a light yellow oil: R_f = 0.52 (20% EtOAc/hexanes)**;** $[\alpha]_D^{27}$ = −1.43 (*c* 0.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.3 Hz, 4H), 7.42–7.33 (m, 6H), 5.88–5.72 (m, 1H), 5.08–4.91 (m, 3H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.57 (d, *J* = 6.9 Hz, 1H), 3.86–3.78 (m, 1H), 3.63–3.51 (m, 1H), 3.38 (s, 3H), 2.27–2.02 (m, 5H), 1.67–1.14 (m, 8H), 1.04 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.72, 170.59, 138.09, 135.88, 134.82, 134.43, 129.50, 129.42, 127.52, 127.41, 115.06, 115.00, 96.68, 95.97, 77.70, 77.48, 74.90, 74.36, 69.38, 69.20, 55.89, 55.81, 39.36, 39.20, 29.95, 29.82, 29.64, 29.58, 29.42, 27.04, 23.31, 23.15, 21.74, 21.13, 19.28; IR (thin film) 2931, 2857, 1736, 1373, 1240, 1105 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{46}NaO_5Si$ $(M + Na)^+$ 549.3012, found 549.3012.

(5*S*,10*R*)-10-Hydroxy-5-(methoxymethoxy)undec-1-en-6-yl acetate (*epi*-9): Alcohol *epi*-**9** was prepared from compound **46** (315.1 mg, 0.60 mmol) using the general procedure for desilylation. The crude residue was purified by column chromatography (10–30% EtOAc/hexanes) to give alcohol *epi*-**9** (130.9 mg, 76%) as a colorless oil: R_f = 0.22 (30% EtOAc/hexanes); $[\alpha]_D^{27}$ = −6.58 (*c* 0.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89–5.73

(m, 1H), 5.08–4.97 (m, 3H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.79 (sext, *J* = 6.0 Hz, 1H), 3.68–3.57 (m, 1H), 3.39 (s, 3H), 2.30–2.11 (m, 2H), 2.08 (s, 3H), 1.72–1.38 (m, 8H), 1.18 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.89, 170.80, 138.00, 137.96, 115.05, 96.61, 95.95, 77.65, 77.51, 74.80, 74.19, 67.68, 55.88, 55.77, 38.91, 29.84, 29.77, 29.71, 29.60, 29.51, 29.33, 23.45, 21.95, 21.73, 21.13, 21.08; IR (thin film) 3447, 2934, 1736, 1373, 1243, 1035 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}NaO_5$ $(M + Na)^+$ 311.1834, found 311.1834.

(2*S*,7*S*)-6-Acetoxy-7-(methoxymethoxy)undec-10-en-2-yl 2,4-bis(ethoxymethoxy)-6-vinylbenzoate (47): Ester **47** was prepared from alcohol *epi*-**9** (170.6 mg, 0.60 mmol) and benzoic acid **8b** (178.6 mg, 0.60 mmol) using the general procedure for Mitsunobu esterification. The crude residue was purified by column chromatography (10–20% EtOAc/hexanes) to give ester **47** (240.6 mg, 70%) as a light yellow oil: R_f = 0.58 (50% EtOAc/hexanes); $[\alpha]_D^{27}$ = +1.00 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (d, *J* = 2.1 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.69 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.88–5.77 (m, 1H), 5.71 (d, *J* = 17.4 Hz, 1H), 5.33 (d, *J* = 10.8 Hz, 1H), 5.23 (s, 2H), 5.20 (s, 2H), 5.18–5.13 (m, 1H), 5.08–4.97 (m, 3H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.59 (d, *J* = 6.9 Hz, 1H), 3.71 (qd, *J* = 6.9, 1.8 Hz, 4H), 3.66–3.55 (m, 1H), 3.39 (s, 3H), 2.31–2.09 (m, 2H), 2.05 (s, 3H), 1.78–1.38 (m, 8H), 1.33 (d, *J* = 6.3 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.65, 170.55, 167.37, 158.88, 155.31, 137.97, 137.18, 133.43, 118.18, 117.14, 115.08 115.02, 105.74, 103.14, 96.68, 96.05, 93.40, 93.08, 77.73, 77.49, 74.78, 74.06, 71.68, 64.38, 64.30, 55.89, 55.78, 35.74, 29.95, 29.86, 29.61, 29.55, 29.12, 21.76, 21.59, 21.09, 19.97, 15.05, 15.02; IR (thin film) 2977, 2935, 1733, 1600, 1265, 1151 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{46}NaO_{10}$ $(M + Na)^+$ 589.2989, found 589.2988.

(3*S*,8*S*,*E*)-14,16-Bis(ethoxymethoxy)-8-(methoxymethoxy)-3-methyl-1-oxo-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclotetradecin-7-yl acetate (48): Macrolactone **48** was prepared from ester **47** (55.6 mg, 0.10 mmol) using the general procedure for ring-closing metathesis. The crude residue was purified by column chromatography (10–20% EtOAc/hexanes) to give macrolactone **48** as an inseparable mixture of diastereomers as a light yellow oil (35.2 mg, 65%): R_f = 0.50 (50% EtOAc/hexanes); $[\alpha]_D^{28}$ = +12.50 (*c* 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80–6.50 (m, 3H), 6.22–6.05 (m, 1H), 5.27–4.95 (m, 6H), 4.71 (d, *J* = 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 3.84–3.67 (m, 5H), 3.36 (s, 3H), 2.38–2.28 (m, 2H), 2.07 (s, 3H), 1.93–1.51 (m, 8H), 1.34 (t, *J* = 6.6 Hz, 3H), 1.25–1.18 (m,

6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.61, 167.63, 167.42, 158.81, 158.76, 155.53, 155.02, 137.89, 137.64, 134.20, 134.06, 128.11, 127.08, 117.96, 117.27, 107.43, 106.65, 102.58, 102.34, 96.64, 96.06, 93.45, 93.28, 93.00, 76.66, 75.66, 73.85, 73.74, 71.99, 71.18, 64.36, 64.28, 55.69, 35.84, 35.79, 30.41, 29.40, 28.21, 27.06, 26.86, 21.88, 21.22, 20.95, 20.88, 20.67, 15.07, 15.01; IR (thin film) 2970, 2934, 1731, 1600, 1248, 1150 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{42}NaO_{10}$ $(M + Na)^+$ 561.2676, found 561.2676.

Macrolactone alcohols 49: Macrolactone alcohols **49** were prepared from macrolactone acetate **48** (30.2 mg, 0.06 mmol) using the general procedure for methanolysis. The crude residue was purified by column chromatography (20–40% EtOAc/hexanes) to give a major diastereomer (12.2 mg, 44%) and a minor diastereomer (9.20 mg, 33%) of alcohols **49**.

Major diastereomer of alcohol 49. Colorless oil**:** R_f = 0.27 (50% EtOAc/hexanes); $[\alpha]_D^{29}$ = +7.69 (*c* 0.26, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (d, *J* = 2.1 Hz, 1H), 6.74 (d, *J* = 2.1 Hz, 1H), 6.52 (d, *J* = 16.2 Hz, 1H), 6.19 (dt, *J* = 16.2, 6.3 Hz, 1H), 5.26–5.17 (m, 5H), 4.72 (d, *J* = 6.6 Hz, 1H), 4.65 (d, *J* = 6.6 Hz, 1H), 3.95–3.92 (m, 1H), 3.71 (qd, *J* = 6.9, 1.8 Hz, 5H), 3.40 (s, 3H), 2.35–2.31 (m, 2H), 1.89–1.42 (m, 8H), 1.33 (d, *J* = 6.6 Hz, 3H), 1.22 (t, *J* = 7.2, Hz, 3H), 1.21 (t, *J* = 7.2, Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.70, 158.76, 155.06, 137.58, 134.05, 126.70, 118.11, 106.57, 102.44, 96.62, 93.34, 93.06, 79.43, 72.27, 71.43, 64.37, 64.31, 55.80, 36.33, 32.52, 26.70, 25.24, 21.94, 20.75, 15.08, 15.01; IR (thin film) 3501, 2933, 1721, 1600, 1264, 1149 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}NaO_9$ $(M + Na)^+$ 519.2570, found 519.2570

Minor diastereomer of alcohol 49. Light yellow oil; R_f = 0.35 (50% EtOAc/hexanes); $[\alpha]_D^{29}$ = +64.30 (*c* 0.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 2.1 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 6.58 (d, *J* = 16.2 Hz, 1H), 6.14 (dt, *J* = 16.2, 6.3 Hz, 1H), 5.30–5.17 (m, 5H), 4.70 (s, 2H), 3.72 (q, *J* = 6.9 Hz, 4H), 3.57–3.47 (m, 2H), 3.41 (s, 3H), 2.38–2.31 (m, 2H), 1.94–1.49 (m, 8H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.72, 158.70, 155.30, 137.39, 134.39, 127.23, 117.67, 107.11, 102.46, 97.15, 93.40, 93.03, 81.99, 71.78, 70.85, 64.41, 64.34, 55.82, 35.71, 31.66, 29.70, 27.90, 26.74, 20.72, 20.62, 15.10, 15.03; IR (thin film) 3482, 2930, 1720, 1600, 1261, 1151 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}NaO_9$ $(M + Na)^+$ 519.2570, found 519.2570.

(3*S*,8*S*,*E*)-14,16-Bis(ethoxymethoxy)-8-(methoxymethoxy)-3-methyl-3,4,5,6,9,10-hexahydro-1H-benzo[c][1]oxacyclotetradecine-1,7(8H)-dione (50): Ketone **50** was

prepared from the major diastereomer of alcohol **49** (12.2 mg, 0.024 mmol) and the minor diastereomer of alcohol **49** (9.2 mg, 0.02 mmol) using the general procedure for DMP oxidation. The crude residue was purified by column chromatography (20% EtOAc/hexanes) to give ketone **50** (10.7 mg, 88% from the major diastereomer of alcohol **49**, 7.2 mg, 79% from the minor diastereomer of alcohol **49**) as a light yellow oil: R_f = 0.50 (50% EtOAc/hexanes); $[\alpha]_D^{29}$ = +60.01 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 2.1 Hz, 1H), 6.74 (d, *J* = 2.1 Hz, 1H), 6.37 (d, *J* = 15.6 Hz, 1H), 6.05 (ddd, *J* = 15.6, 8.7, 4.8 Hz, 1H), 5.22–5.17 (m, 5H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.58 (d, *J* 6.9 Hz, 1H), 4.11–4.08 (m, 1H), 3.71 (q, *J* = 7.2 Hz, 4H), 3.33 (s, 3H), 2.76–1.63 (m, 10H), 1.34 (d, *J* = 6.3 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.48, 167.65, 158.90, 155.14, 137.32, 133.63, 127.73, 117.90, 106.37, 102.49, 96.23, 93.46, 93.08, 81.20, 71.55, 64.44, 64.33, 55.90, 39.78, 34.78, 29.99, 27.99, 20.91, 20.62, 15.07, 14.99; IR (thin film) 2931, 1719, 1599, 1261, 1150, 1106 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{40}NaO_9$ $(M + Na)^+$ 519.2570, found 519.2570.

5'β-Hydroxyzearalenone (6): 5'β-Hydroxyzearalenone (**6**) was prepared from ketone **50** (17.6 mg, 0.035 mmol) using the general procedure for deprotection of alkoxy ether group. The crude residue was purified by column chromatography (20–40% EtOAc/hexanes) to give 5'β-Hydroxyzearalenone (**6**) (8.9 mg, 75%) as a white solid: R_f = 0.27 (50% EtOAc/hexanes); mp 150–153 °C; $[\alpha]_D^{28}$ = −97.42 (*c* 0.15, acetone); CD (c 1.64x10^{-3} M, MeOH) λ_{max}: 266 nm (Δε = –55.29); ^{1}H NMR (300 MHz, acetone-d_6) δ 11.97 (s, 1H), 9.36 (brs, 1H), 7.02 (d, *J* = 15.3 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 5.84 (ddd, *J* = 15.3, 10.2, 3.6 Hz, 1H), 5.16–5.07 (m, 1H), 4.35–4.30 (m, 1H), 4.22 (brd, *J* = 6.0 Hz, 1H), 2.97–2.85 (m, 1H), 2.50–2.35 (m, 1H), 2.33–2.14 (m, 1H), 2.02–1.87 (m, 1H), 1.93–1.69 (m, 6H), 1.39 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 211.03, 171.83, 166.09, 163.12, 144.43, 133.04, 132.10, 108.99, 103.36, 102.36, 73.70, 73.50, 39.07, 35.02, 31.19, 28.71, 21.14, 19.69; IR (thin film) 3250, 2932, 1708, 1642, 1312, 1260 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}NaO_6$ $(M + Na)^+$ 357.1314, found 357.1315.

Cytotoxicity Assay: Breast adenocarcinoma MCF-7 and MDA-MB-231, and cervical carcinoma SiHa, HeLa and C33A cell lines were obtained from American Type Culture Collection (ATCC, USA); hepatoma HepG2, and colorectal carcinoma HCT116 cell lines were kindly provided by Prof. Dr. Mathurose Ponglikitmongkol (Mahidol University,

Thailand), and the non-cancer Vero cell line was kindly provided by Dr. Sittirak Roytrakul (The National Center for Genetic Engineering and Biotechnology, Thailand). All cell lines were maintained in Dulbecco's modified Eagle's (DMEM) medium supplemented with 10% fetal bovine serum, 100 U/mL penicillin and 100 µg/mL streptomycin at 37 °C in humidified atmosphere containing 5% CO_2. All culture reagents were purchased from Thermo Fisher Scientific (Gibco®,USA). Log phase cells were seeded onto 96-well culture plate (Costar®, Corning Incorporated, USA) at a density of 2.5 or 5×10^3 cells/well and incubated overnight. After that, cells were exposed to various concentrations of compounds (0-200 µM; 0.2% (v/v) DMSO). After 72h of incubation, cell viability was determined by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (Applichem, Germany) assay as previously described.[25] Each experiment was performed in triplicate and was repeated three times. Data was expressed as %cell viability and IC_{50}values (the concentration needed for 50% cell growthinhibition) relative to the untreated cells (0.2% (v/v) DMSO) (means ± SD). Cisplatin and doxorubicin (Pfizer, Australia) were used as positive controls.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for all other compounds, comparison of ^{1}H and ^{13}C NMR data for natural and synthetic **5** and **6**, copies of the ^{1}H NMR and ^{13}C NMR spectra of all new compounds, CD spectra of compounds **5** and **6** and HPLC traces.

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Keywords: Total synthesis • Resorcylic acid lactone • 5′-hydroxyzearalenone • 5′β-hydroxyzearalenone • Cytotoxic activity

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